NOVEMBER 1958
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Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

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2. Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico* 47:305, Aug., 1955.

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Editorial

Strokes—Progress and Problems

IT IS attractive to contemplate that when and if the prevention and reversal of atherosclerosis is achieved, most cerebrovascular disease will fade from the medical scene together with coronary and peripheral arterial disease. Unfortunately we have little to be complacent about in this regard. Most of the so-called epidemiologic studies dealing with the relationship of diet to atherosclerosis are inadequate and at best only suggestive. For example, the studies showing that death from atherosclerotic heart disease is rare in the Bantu natives have been largely based on autopsy findings and hospital records. The results at first thought appear valid, but to be valid they must be accurate and meaningful. Certain little-known factors may, however, render their interpretation doubtful. For example, transportation for natives in Bantu country is often difficult and the distances are great. This could mean that many patients suffering sudden death, of which cardiovascular diseases are the commonest cause, fail to reach the hospitals, whereas those suffering from diseases that do not kill suddenly do reach the hospitals. Such a situation may well affect the hospital and autopsy statistics. The errors are compounded on a national level by the fact that the cause of death of a Bantu dying of natural causes need not be established or recorded under the law. Recently Lawrie and Woods[1] published autopsy data that cast doubt on the conclusion that atherosclerosis is rare in the Bantu. On the basis of just under 2,000 autopsies they conclude that atherosclerosis is common in the aorta and that it is fairly common in the cerebral vessels. The significance, in terms of the development of atherosclerosis, of the fact that these natives exist on a diet low in saturated fats is thus open to question. If atherosclerosis is in reality not rare in the Bantu natives, then what is the significance of the reported low serum cholesterol readings obtained from this group? It has been claimed that the Japanese have a low incidence of deaths from heart disease, but a fairly high incidence of cerebral vascular disease. This illogical paradox may well be explained by the long-standing custom among the Japanese of recording the cause of sudden deaths as apoplexy. Some national populations arranged according to the amount of intake of saturated fats may show a parallel relation between this factor and death from heart disease. However, as Yerushalmy and Hilleboe[2] have pointed out, 22 countries, selected at random, fail to confirm this relationship; indeed they found the relationship of the intake of protein to deaths from heart disease was closer. Because of the weakness in such statistics, it behooves us to maintain a healthy scepticism and to lean more heavily on solid statistical material such as that emanating from the Framingham Study of the U. S. Public Health Service.[3, 4] In most studies the great emphasis has been on atherosclerosis of the coronary arteries and the aorta. It is to be hoped that before this study is terminated, the details of the cerebral vascular and other peripheral vascular pathology will be as complete as those relating to the coronary arteries and the aorta.

It has now been shown as a result of the work of Ahrens and his co-workers[5–8] and Malmros[9, 10] that the serum cholesterol level of subjects can be reduced by sharply reducing the intake of saturated fats and substituting for these unsaturated fats with high-iodine indices and linoleic acid content. Whether this will have any effect on the further progression of atherosclerosis, or, more specifically, the incidence of strokes, is unknown. Many patients have been indulging themselves with their usual fat intake and taking in addition doses of safflower oil in the illusion that this will in some way reduce their cholesterol level.[11] Double-blind studies in our laboratory with 24 young men who continued on their regular diet but took the maximum dosage of safflower oil recommended, and in most cases tolerated, (15 ml. 65 per cent safflower oil emulsion 5 times daily—total 75 ml. a day), failed to show any decrease in the serum cholesterol levels as compared with controls using an inert placebo preparation.

Another aspect of fat ingestion that is pertinent to our present problem is the question whether or not a large fat meal will increase the clotting tendency in the blood, and, by inference, the risk of thrombosis. Waldron and Duncan[12, 13] and Buzina and Keys[14] have obtained results which they think justify the position that such a relation exists. Two teams of workers in our own laboratory have failed to confirm this finding.[15] Sheehy and Eichelberger[16] have recently published results with a more objective method of thrombelastography that show no significant increase in clotting tendency following the ingestion of a high-fat meal. Doubtless the last has not been heard on this subject.

Although hypertension is a very important factor in the production of strokes due to hemorrhage, and although we now have potent drugs for the reduction of blood pressure, the situation is still not ideal. After a massive cerebral hemorrhage it is too late to accomplish much by lowering the blood pressure. Therefore, our attention must be directed at trying to prevent such a critical development. However, this should be undertaken with great caution. Too rapid or profound lowering of the blood pressure may result in decrease or cessation of blood flow through narrowed atherosclerotic arteries with the subsequent development of an ischemic pattern and signs of a stroke. This may be transient, or it may be irreversible and thus, once more, the physician is placed on the horns of a dilemma. Renal dysfunction on the same basis may further complicate this picture.

The diagnosis of the location, size, and exact pathologic status of lesions producing the clinical manifestations of strokes is admittedly difficult, but often it is clear enough to proceed with suitable therapy. The excellent descriptions of carotid and basilar artery thromboses by Millikan and co-workers[17–19] and by Fisher,[20] have helped to clarify this picture. Occlusion of the cerebral arteries and other vessels penetrating the brain present a greater challenge. A persistent problem, now more important than ever before, is the degree of hemorrhage that may be present in an infarcted area due to a thrombosis or embolism. In the past, therapy for strokes presented no problem. There was none. Today, however, with the advent of new therapeutic agents, notably anticoagulants, enzymes such as plasmin, and new surgical technics, the clinician can no longer treat his patient with "skillful neglect," but is forced to undertake most careful study and analysis to determine whether the new therapeutic approaches may be helpful or even life-saving. These advances have resulted in much greater interest and improved general care, but have they improved the outlook for the patient? Even at this early stage, for certain individual cases, the answer can be given in the affirmative. For example, there is substantial evidence that the anticoagulant drugs are effective in decreasing the risk that transient episodes due to partial occlusion of the carotid or basilar arteries will progress to massive and permanent neurologic deficit. Accumulating evidence also indicates that after the first stroke due to either thrombosis or embolism the risk of additional strokes and other thromboembo-

complications will be markedly diminished by the long-term use of anticoagulants.

The value and the risk of these drugs during the acute phase of a stroke due to occlusion of the cerebral vessels and other branches penetrating the brain tissue are presently under intensive study in several institutions. As implied above, the amount of bleeding into the infarcted areas is difficult to evaluate. This aspect of the problem requires further study. The use of enzymes to hasten the dissolution of thrombi, such as fibrinolysin (plasmin), has opened a new approach that is worthy of intensive study. Used together with anticoagulants, they may offer a potentially important forward step.

Surgery is also on the march. Striking results have occurred by tapping subdural or extrameningeal hemorrhages, but so far the results of surgery for massive brain hemorrhage have been disappointing. However, with the use of hypothermia, this approach has, on a few occasions, been encouraging. Surgery for intracranial aneurysms and arteriovenous anastomoses has occasionally been successful, but like surgery for similar conditions elsewhere, the long-range results are often unsatisfactory. Among the most encouraging new steps are the use of synthetic prostheses to replace segments of carotid arteries occluded in sharply localized sites, and thromboendarterectomy of these same vessels. When one recalls the status of heart surgery 15 years ago, great advances in vascular surgery of the brain seem clearly visible on the horizon.

After the acute phase of the stroke, 2 main objectives constitute the responsibility of the physician: (1) Rehabilitation from the damage already suffered. This goal is being widely and intensively pursued, but carefully controlled evaluation of the results has, as yet, not been carried out. The question to be answered is whether or not the expense and work involved in such a program really increase the rate and degree of improvement, or whether this is controlled by the motivation of the patient himself, which, in turn, may be dependent on the home and work life that he has to face in the future. A controlled study to answer this difficult but important question is in progress. (2) Prevention of future strokes that often produce more serious and permanent or fatal damage. The judicious use of anticoagulants and antihypertensive agents, serious efforts to control cardiac rhythm, the avoidance of obesity and excessive physical and emotional stress, all contribute to such a program. Formerly the physician could rest his oars after the initial crisis had subsided. Now his responsibility continues during the subsequent history of the patient. With these and other technics opening up new vistas, we can anticipate advances which, however, are likely to require ever more diligence and skill by the physician.

IRVING S. WRIGHT

REFERENCES

1. LAURIE, W., AND WOODS, J. D.: Atherosclerosis and its cerebral complications in the South African Bantu. Lancet **1**: 231, 1958.
2. YERUSHALMY, J., AND HILLEBOE, H. E.: Fat in the diet and mortality from heart disease. New York J. Med. **57**: 2343, 1957.
3. DAWBER, T. R., MEADORS, G. F., AND MOORE, F. E., JR.: Epidemiological approach to heart disease: Framingham Study. Am. J. Pub. Health **41**: 279, 1951.
4. STOKES, JOSEPH, III, AND DAWBER, T. R.: Rheumatic Heart Disease in the Framingham Study. New England J. Med. **255**: 1228, 1956.
5. AHRENS, E. H., JR., DOLE, V. P., AND BLANKENHORN, D. H.: The use of orally fed liquid formulas in metabolic studies. Am. J. Clin. Nutrition **2**: 336, 1954.
6. —, HIRSCH, JULES, INSULL, W., JR., TSALTAS, T. T., BLOMSTRAND, R., AND PETERSON, M. L.: Dietary control of serum lipids in relation to atherosclerosis. J.A.M.A. **164**: 1905, 1956.
7. —, INSULL, W., BLOMSTRAND, R., HIRSCH, J., TSALTAS, T. T., AND PETERSON, M. L.: The influence of dietary fats on serum lipid levels in man. Lancet **270**: 521, 1956.
8. —: Dietary fats and human lipid levels. *In* Chemistry of Lipids as Related to Atherosclerosis. I. H. Page, ed. Springfield, Ill., Charles C Thomas, 1958.
9. MALMROS, H., AND WIGAND, G.: Treatment of hypercholesterolemia. Minnesota Med. **38**: 863, 1955.

10. —, AND —: The effect upon serum cholesterol of diets containing different fats. Lancet **2**: 1, 1957.
11. PERKINS, R., WRIGHT, I. S., AND GATJE, B. W.: Effect of safflower oil emulsion on serum cholesterol levels in young adult males: Its use as a supplement to a normal diet. J.A.M.A. **166**: 2132, 1958.
12. DUNCAN, G. G., AND WALDRON, J. M.: The effect of ingested fat on blood coagulation. Tr. A. Am. Physicians **42**: 179, 1949.
13. WALDRON, J. M., AND DUNCAN, G. G.: Variability of the rate of coagulation of whole blood. Am. J. Med. **17**: 365, 1954.
14. BUZINA, R., AND KEYS, A.: Blood coagulation after a fat meal. Circulation **14**: 854, 1956.
15. BORRERO, J., SHEPPARD, E., AND WRIGHT, I. S.: Further experiences with blood coagulation after fat meals and carbohydrate meals. Circulation **17**: 936, 1958.
16. SHEEHY, T. W., AND EICHELBERGER, J. W.: Alimentary lipemia and the coagulability of blood. Analysis by thrombelastography and silicone clotting time. Circulation **17**: 927, 1958.
17. MILLIKAN, C. H., SIEKERT, R. C., AND SCHUCK, R. M.: Studies in cerebrovascular disease. III. Use of anticoagulant drugs in treatment of insufficiency or thrombosis within basilar arterial system. Proc. Staff Meet., Mayo Clin. **30**: 116, 1955.
18. —, —, AND —: Studies in cerebrovascular disease. V. Use of anticoagulant drugs in treatment of intermittent insufficiency of internal carotid arterial system. Proc. Staff Meet., Mayo Clin. **30**: 578, 1955.
19. —, —, AND WHISNANT, J.: Anticoagulant therapy in cerebral vascular disease: Current status. J.A.M.A. **166**: 587, 1958.
20. FISHER, M.: Comments. *In* Wright, I. S., and Luckey, E. H.: Cerebral Vascular Diseases: Trans. of Conf., Princeton, N. J., January 1954. New York, Grune & Stratton, Inc., 1955, p. 39.
21. —: Intermittent cerebral ischemia; basilar and carotid artery disease; the slow stroke; the recurrent stroke. *In* Wright, I. S., and Millikan, C. H.: Cerebral Vascular Disease: Trans. of Conf., Princeton, N. J., January 1957. New York, Grune & Stratton, Inc. In press.

Letter of Jenner to Heberden

"The importance of the coronaries, and how much the heart must suffer from their not being able duly to perform their functions (we can not be surprised at the painful spasms), is a subject I need not enlarge upon, therefore shall just remark that it is possible that all the symptoms may arise from this one circumstance.

"As I frequently write to Mr. H. I have been some time in hesitation respecting the propriety of communicating the matter to him, and should be exceedingly thankful to you, sir, for your advice upon the subject. Should it be admitted that this is the cause of the disease, I fear the medical world may seek in vain for a remedy, and I am fearful (if Mr. Hunter should admit this to be the cause of the disease) that it may deprive him of the hopes of a recovery."—WILLIAM OSLER, M.D. *Lectures on Angina Pectoris and Allied States*, 1897.

Work and Heart Disease

I. A Physiologic Study in the Factory

By Amasa B. Ford, M.D., and Herman K. Hellerstein, M.D.

Sixty-two factory workers, 36 with heart disease, and 26 healthy control subjects, were studied during a typical day's work. Observations of energy expenditure, pulmonary ventilation, pulse rate and electrocardiogram are reported and analyzed in relation to the type of work, the influence of heart disease, and possible objective evidence of fatigue.

New understanding of the natural history of heart disease and better methods of treatment are reducing the aura of fear traditionally surrounding the cardiac patient. At the same time, modern technology is steadily lowering the physical demands of factory work, so that it is now evident that a majority of urban patients with heart disease can work safely.[1] The physician, who is increasingly called upon to prescribe activity for his patients with heart disease, needs specific information about the stress of daily activities on which to base his advice. Artificial work situations, such as the Master 2-step test or treadmill exercise, involve high-energy expenditure for short periods of time and cannot simulate actual working conditions unless the doctor has specific knowledge of the demands of the patient's job.[2, 3]

Many measurements of the energy cost of individual activities and a few studies of energy expenditure during several hours or days have been collected by Passmore and Durnin.[4] However, these studies are of normal people in other countries and under other economic conditions. No studies have been published of working energy expenditure of patients with heart disease. The present study therefore was designed to measure the energy expenditure of factory workers with heart disease, to observe various aspects of cardiovascular function under actual working conditions, and to compare in each particular the workers with heart disease with their healthy co-workers.

Methods and Material

Subjects. Sixty-two subjects were studied on the job. Thirty-six had recognized heart disease and 26 were normal control subjects. A control subject was matched to each cardiac subject whenever a healthy worker of comparable age and skill could be found performing the same job in the same industrial plant.

The subjects with heart disease were employees of 3 large Cleveland manufacturing firms and had come to the attention of the industrial physician in the course of employment physical examinations, illness at work, or from reports of private physicians following illness. The diagnosis of heart disease was confirmed by a complete medical history, physical examination and standard 12-lead electrocardiogram. Twenty-four of the 36 patients with heart disease were evaluated at the Work Classification Clinic of the Cleveland Area Heart Society where additional laboratory studies including fluoroscopic examination, ballistocardiogram and the Master 2-step exercise test were made.

All the subjects were men, except for 1 woman, who had arteriosclerotic heart disease. Twenty-five patients had arteriosclerotic heart disease, of whom 20 had old myocardial infarcts confirmed by electrocardiogram. Four subjects had hypertensive cardiovascular disease, 5 rheumatic heart disease, 1 syphilitic aortitis and aneurysm, and 1 possible congenital heart disease. It is probable that most of the employees with symptomatic coronary artery disease in these 3 industries were studied. Undoubtedly many individuals with varying degrees of hypertension and some with asymptomatic rheumatic heart disease were not included. Twelve of the cardiac subjects fell into class I of the New York State Heart Association,[5] 19 into class II and 5 into class III. Ten of the 36 patients were taking digitalis at the time of

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TABLE 1.—*Types of Jobs Studied*

Miscellaneous (4 cardiacs, 2 controls)
Boxmaker
Laundry crib supervisor
Planning clerk
Tool crib attendant
Bench Workers (8 cardiacs, 7 controls)
Assembler
Clutch tester
Electronics tester
Gauge setter
Light assembler (2 subjects)
Millwright
Stamper
Foremen (7 cardiacs, 5 controls)
Foreman
Inspector
Lead man (foreman)
Maintenance supervisor
Shift foreman
Supervisor (2 subjects)
Machine Operators (7 cardiacs, 5 controls)
Drill press operator (2 subjects)
Scarfing machine operator
Set-up burnishing press
Stub lathe operator
Tool grinder
Turret lathe operator
Maintenance Workers (7 cardiacs, 4 controls)
Janitor
Maintenance electrician
Matron
Painter
Plant guard
Stationary engineer
Welder
Warehousemen (3 cardiacs, 3 controls)
Stock picker

the study. The average age of the cardiac subjects was 51 years, with a range of 24 to 70 years, while the control group averaged 42 years, ranging from 18 to 65 years.

The subjects were found to be working in every major department of the 3 companies. These plants manufacture light and medium weight metal products, including electric motors and switches, automobile and airplane parts, bearings, and nonferrous metal products. They employ a total of 8,500 people and are representative of the type of industry that employed one third of the working population of Cuyahoga County (Cleveland) in a 1946 survey.[6] The types of jobs varied considerably in skill and energy expenditure (table 1).

Methods. Each subject reported to the company dispensary 15 minutes before the shift on a typical working day. The purpose and methods of the study had been explained to each subject. Height and weight were measured, and 4 copper electrodes were taped in place on the chest in the V$_4$ and V$_5$ positions on right and left sides. Lead wires passed through the shirt collar to a socket attached to the subject's belt, where they could be connected to a Sanborn direct-writing electrocardiograph when desired. A pedometer was adjusted and fastened to the subject's belt. An Air Force half-face oxygen demand mask was carefully fitted and arranged to permit inhalation of room air. From the mask expired air passed through a Plexiglass valve and rubber tubing to the Kofranyi-Michaelis respiratory meter.[7] The meter, which together with mask and tubing weighs 3.6 Kg., was either worn like a knapsack or placed on a table during sedentary observations. While the subject was becoming accustomed to the mask, observations were made of blood pressure and electrocardiogram. A 5-minute aliquot of expired air was then collected, and pulmonary ventilation was read from the meter to determine resting oxygen consumption. Respiratory rate was measured during the collection period. The mask and meter were then removed, but the electrodes were left in place, and the subject was accompanied to his place of work.

A detailed log was kept of the exact duration of each activity in which the subject engaged during the day. Five-minute samples of expired air were collected for the purpose of measuring energy expenditure during each activity, after at least 5 minutes of performing that activity while wearing the mask and meter. Electrocardiograms and respiratory rate were recorded as the sample was being taken, and blood pressure was measured either during or immediately after the determination. At least 3 observations were made of energy expenditure at rest (before work, in mid-shift and just before the end of the shift). Multiple observations were made on any activity that occupied more than an hour of the subject's time. Five to 9 (average, 7) samples of expired air were collected during the day. The specific requirements of the study took about an hour from the regular working time, but in no case did a worker fail to meet a quota for the day or show other objective evidence of hampered efficiency or productivity on account of the study.

TABLE 2.—*Average Rates of Energy Expenditure (Calories Per Minute)*

	36 Cardiacs		26 Controls	
	Average	S.D.	Average	S.D.
At rest	1.30	*0.25*	1.40	*0.30*
During shift	1.97	*0.48*	2.13	*0.45*
During actual work	2.29	*0.64*	2.51	*0.68*

Samples of expired air were transferred immediately from the butyl rubber collecting bag to glass sample tubes, where they were stored under positive pressure of mercury and thus transported to the laboratory. Analyses for carbon dioxide and oxygen content were performed with the Scholander micro gas analyzer.[8] Duplicate determinations gave a mean difference of 0.03 volume per cent (S.D. of the difference = 0.06 volume per cent) for carbon dioxide and 0.03 volume per cent (S.D. of the differences = 0.07 volume per cent) for oxygen. The volume measurements of the respiratory meter, compared with a 100-liter Tissot spirometer at rates of flow of from 10 to 50 liters per minute, gave a mean error of 1.3 per cent of the total. The maximum resistance to breathing offered by the meter at these flows was 2.0 cm. of water. Oxygen consumption (milliliters per minute) was taken as 10 times the product of ventilation (liters per minute) and oxygen utilization (per cent of oxygen in room air minus per cent of oxygen in expired air), and converted to energy expenditure (in kilogram calories per minute) according to the data of Cathcart and Cuthbertson.[9] All volumes were reduced to standard conditions (0 C., 760 mm. Hg, dry). Rates of energy expenditure were expressed without deduction of a basal or resting value. Energy expenditure was not divided by body surface area, since these quantities have not been shown to bear a constant relationship during different types of activity.

OBSERVATIONS

Energy Expenditure

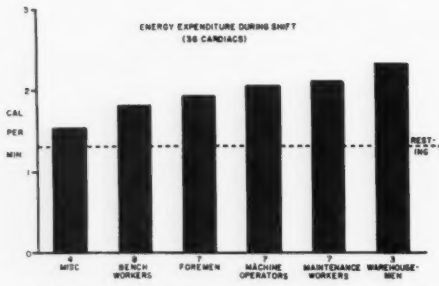
The average rate of energy expenditure of workers with heart disease was 1.97 calories per minute or a total of 997 calories during the 8½ hour work shift (table 2). A higher rate of energy expenditure, 2.29 calories per minute, obtained during actual working time. The figures for the control subjects were higher but were not significantly different as judged by the t test, and a probability level of 5 per cent ($t = 1.06$, $p = < 0.4$).

TABLE 3.—*Age and Blood Pressure*

	36 Cardiacs		26 Controls		
	Avg.	S.D.	Avg.	S.D.	*p*
Age (years)	51	*9.4*	42	*12.3*	<.02
Systolic blood pressure at rest (mm. Hg)	136	*22*	122	*18*	<.05
Diastolic blood pressure at rest (mm. Hg)	81	*10*	81	*13*	—
Maximum systolic blood pressure at work (mm. Hg)	153	*29*	134	*20*	<.02
Maximum diastolic blood pressure at work (mm. Hg)	89	*10*	88	*13*	—

The energy cost of individual jobs increased as the work involved the use of progressively larger muscle groups (fig. 1). There was a progression from sedentary to ambulatory work and from hand work to work involving leg, trunk and shoulder muscles. The same pattern was evident among the control workers. In both groups there was considerable overlap among categories of work. In many supervisory and maintenance jobs, walking made up the bulk of the energy demand. Twelve subjects walked more than 5 miles during the shift, and 2 walked more than 10 miles. Although the walking was usually intermittent, it required an average energy expenditure of 2.79 calories per minute. The energy cost of this factory work was remarkably low. Only in the maintenance and warehouseman groups were there a few individuals whose average rate of energy expenditure equalled twice the resting level.

Maximum rates of energy expenditure varied from individual to individual but were seldom excessive (fig. 2). The noncardiac workers had slightly higher maximum energy expenditures (average peak of 3.45 calories per minute) than did those with heart disease (average peak of 3.04 calories per minute). However, when each subject was compared with his matched control, the differences were not statistically significant ($t = 1.56$, $p = < 0.2$).



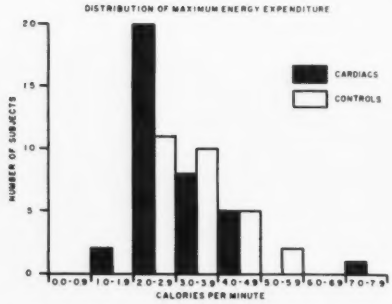


FIG. 1 *Left*. Average rate of energy expenditure during shift of 36 factory workers with heart disease.

FIG. 2 *Right*. Distribution of maximum rates of energy expenditure during factory work for 36 cardiac and 26 control subjects.

Different jobs required different patterns of energy expenditure. In each job the magnitude and duration of energy expenditure and sequence of tasks were consistent and were not modified by the presence of heart disease in the worker. Two basic patterns were observed: (1) a low rate of energy expenditure maintained fairly steadily and (2) high peaks of energy expenditure alternating with inactive periods (fig. 3). The majority of jobs studied resembled the low steady pattern. Only 13 subjects had peaks of energy expenditure above 4.0 calories per minute. The workers took an average of from 9 to 10 breaks during the shift, for an average total of 1¾ hours. This time includes breaks, rest periods and meals, but not time away from work necessitated by the study procedures. Again, no significant difference in the frequency or duration of rest periods was noted in a comparison of the cardiac workers with their controls.

Specific types of heart disease showed no influence on the amount or pattern of energy expenditure when paired subjects and controls were compared within diagnostic categories. In the largest category, that of arteriosclerotic heart disease with previous myocardial infarction, the average rate of energy expenditure was identical for the 23 patients and 17 controls, namely 1.84 calories per minute. The other diagnostic categories were too small (1 to 5 pairs) for significant comparison.

Physiologic Parameters of Cardiovascular Function

The data were next analyzed for evidence of stress, which might distinguish the subject with heart disease from his healthy coworker or which might be considered injurious to the cardiac patient.

Blood Pressure. The average systolic blood pressure at rest and at work was higher in the cardiac group than among the controls, but the diastolic blood pressures were nearly identical. The differences in systolic pressure were statistically significant, probably as a result of the significantly greater age of the group with heart disease rather than the inclusion of patients with hypertension, since there were only 3 of the latter (table 3).

None of the cardiac subjects developed a working blood pressure higher than 184/100 mm. Hg, except 2 patients with hypertension and 2 with aortic insufficiency who developed systolic pressures above this level. The subject whose blood pressure rose to 184/10 mm. Hg at work was a 62-year-old man who had previously recovered from a myocardial infarction and who died suddenly 3 months after the study. None of the control subjects developed a working blood pressure higher than 162/108 mm. Hg except 3 who were found to have previously unrecognized hypertension at rest (diastolic pressure over 100 mm. Hg).

The average maximum increase of blood pressure was 17 mm. Hg systolic and 8 mm.

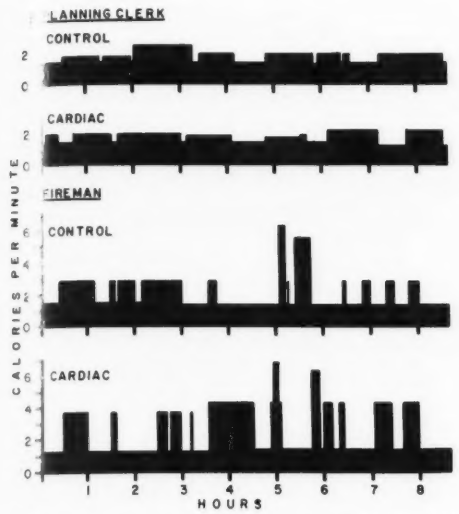


FIG. 3. Pattern of energy expenditure during shift for 2 types of job: *A*. Steady low rate. *B*. Intermittent high rate.

Hg diastolic for the cardiac subjects and slightly less for the controls (table 3). The highest blood pressures recorded during the working day coincided with maximum energy expenditure in only 26 per cent of the total cases and in only 1 of 13 subjects whose blood pressure during work rose above 150 mm. Hg systolic or 100 mm. Hg diastolic. During performance of factory work in the study, therefore, the blood pressure response elicited was small in the normotensive cardiac subject and the controls.

Pulse Rate. The average pulse rate increased from 84 per minute at rest to an average of 102 per minute during work. Sinus tachycardia (over 110 per minute) occurred in 17 subjects (10 controls and 7 cardiac subjects). In 7 subjects the sinus rate reached 120 per minute or more. Three were control subjects, all of whom had resting pulse rates of over 100 per minute, 2 had hitherto undetected hypertension, and the third was obese. Two of the 4 cardiac subjects had high resting pulse rates. A third subject developed the highest pulse rate observed (136 per minute). He was a 59-year-old man with rheumatic heart disease and predominant aortic

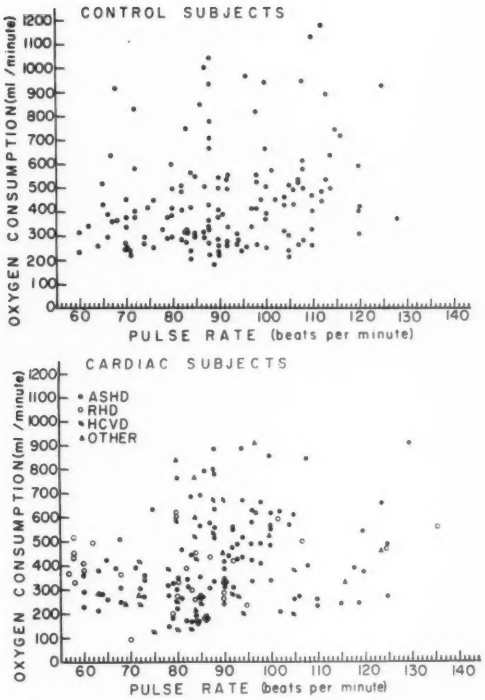


FIG. 4 *Top.* Pulse rate and oxygen consumption, 144 observations on 26 control subjects.

FIG. 5 *Bottom.* Pulse rate and oxygen consumption, 157 observations on 36 subjects with heart disease.

stenosis, classified II C; he died suddenly 4 months after the study. The marked tachycardias were disproportionate to the rate of energy expenditure, since they occurred at rates of 1.8 to 4.3 calories per minute. This type of factory work therefore elicits only a moderate increment in pulse rate. Under the conditions described, a working pulse rate in excess of 120 per minute suggests an undetected or inadequately treated cardiovascular abnormality, sustained anxiety or limited cardiovascular reserve.

Respiration. The average respiratory rate in the cardiac group was 16.4 per minute at rest and 22.7 per minute during maximum exertion, while the average pulmonary ventilation rose from 8.7 liters per minute to 16.9 liters per minute. The figures were slightly higher for the control group, but the differ-

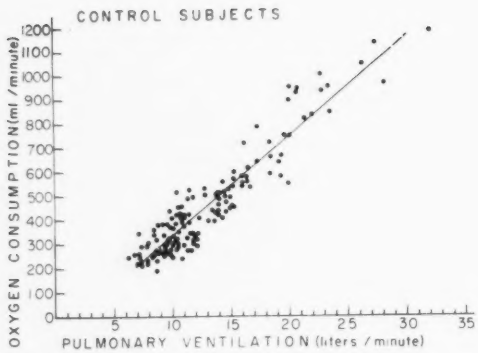


FIG. 6 *Top.* Pulmonary ventilation and oxygen consumption, 144 observations on 26 control subjects ($y = 40.6x - 76.6$).

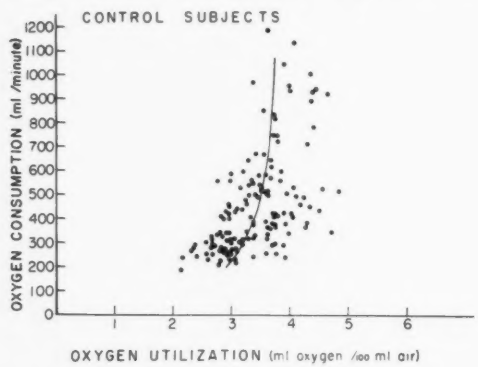


FIG. 7 *Bottom.* Oxygen utilization and oxygen consumption, control subjects ($y = 766z/40.6 - 10z$).

ence was not statistically significant between matched pairs. The highest individual values for respiratory rate and pulmonary ventilation were correlated with high rates of energy expenditure rather than with the specific cardiovascular abnormalities noted to be in association with high blood pressure and pulse rate.

Oxygen utilization is the number of milliliters of oxygen removed from each 100 ml. of air breathed, and equals 10 times the reciprocal of "ventilatory equivalent." Oxygen utilization normally rises with exercise. In the cardiac group it increased from 3.10 ml. of oxygen per 100 ml. of air at rest to 3.85 ml. of oxygen per 100 ml. of air. Both figures were slightly higher in the control group, but the difference was not significant (3.17 ml. of oxygen at rest, 4.00 ml. of oxygen at work). As with pulmonary ventilation, high individual values occurred during high rates of energy expenditure.

Correlation of Physiologic Rates

As the energy expenditure of the human organism increases, the rates of the rhythmic physiologic processes that facilitate the transport of oxygen and the release of energy also rise. It is of interest to examine the cardiac subjects for inappropriate response of such subsidiary mechanisms as heart rate, pulmonary ventilation, or oxygen utilization at a given level of exertion.

Pulse rate in general increases as energy expenditure rises. At rates of over 5 calories per minute the correlation is good enough that pulse rate has been proposed as an index of energy expenditure.[10] Figures 4 and 5 show clearly that at oxygen consumptions below 1 liter per minute (approximately 5 calories per minute), there is extremely poor correlation between pulse rate and oxygen consumption, both for control and cardiac subjects. At these relatively low levels of exertion other factors such as emotion, temperature and interindividual variation probably influence pulse rate so greatly as to make it useless as a criterion of energy expenditure. In the present study the maximum pulse rate coincided with the maximum rate of energy expenditure in only 35 per cent of the cases.

Pulmonary ventilation also increases with oxygen consumption. Here, as may be seen in figure 6, the correlation is excellent in the range of the current observations, and may be described by a straight line of the form

$$y = a + bx$$

where y is oxygen consumption (ml. per minute), x is pulmonary ventilation (L. per minute), and a and b are constants. The regression line has been calculated by the least-squares method and plotted through the points. We also know from the method of calculation used (indirect calorimetry) that

$$y = 10xz$$

where z is oxygen utilization (ml. of oxygen

absorbed per 100 ml. of air breathed). Substituting, we can express the relationship of oxygen consumption to oxygen utilizaton as

$$y = \frac{10za}{10z - b}$$

This curve has been plotted against the actual data for the control subjects in figure 7. In the range studied, the percentage of oxygen extracted from air rapidly approaches a maximum at low rates of energy expenditure. Oxygen utilization would therefore be a poor index of energy expenditure.

In figure 8 pulmonary ventilation has been plotted against oxygen consumption for the subjects with arteriosclerotic heart disease, hypertensive cardiovascular disease and rheumatic heart disease, and the appropriate regression lines have been entered. None of the lines differs significantly from that calculated for the control subjects (fig. 6). The subjects with rheumatic heart disease have a somewhat higher pulmonary ventilation and lower oxygen utilization at a given level of oxygen consumption than do the normal subjects or the patients with arteriosclerotic heart disease. Such a tendency to inefficient extraction of oxygen has been shown[2] to differentiate subjects with mitral stenosis from normal subjects at an oxygen consumption of 1,500 ml. of oxygen per minute and may be the result of limited cardiac output. It should be emphasized, however, that in the present study, at low rates of energy expenditure, this difference is not statistically significant.

Thus, there is no evidence in the present study that workers with compensated heart disease are compelled to make any greater demands upon their reserves in terms of pulse rate, pulmonary ventilation or oxygen utilization in order to perform this type of factory work than are their healthy co-workers.

Electrocardiographic Changes

There were remarkably few electrocardiographic changes. The method of electrode placement yielded information only in the horizontal plane, i.e., on the x and z axis, equivalent to RV_8, V_4, and V_8.

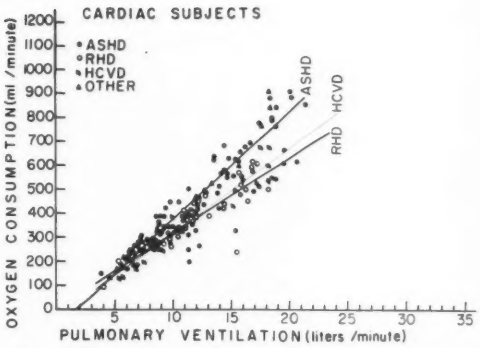


FIG. 8. Pulmonary ventilation and oxygen consumption, cardiac subjects (see text).

In the cardiac group at rest, 2 patients had atrial fibrillation, 4 had ventricular premature beats, and 3 had atrioventricular block (prolonged P-R interval, second-degree block with Wenckebach phenomenon, and complete block).

During work the premature beats persisted but did not increase in frequency; in 4 additional cases rare ventricular premature beats appeared. Three of these 4 subjects had shown an abnormal response to Master's exercise-tolerance test. The premature beats did not appear with maximum energy expenditure. Three subjects showed primary T-wave changes (change in angle QRS-T) during the working day. Two of the 3 subjects also had an abnormal blood pressure response. One of the 2 mentioned had an abnormal maximum pulse rate response and died later at home in bed.

In the subject with second-degree atrioventricular block, ventricular premature beats appeared and the Wenckebach phenomenon became more prominent. In the subject with third-degree atrioventricular block the rate increased from 56 to a maximum of 58 although the energy expenditure ranged from 1.87 to 2.49 calories per minute.

The control subjects all had regular rhythm. Two subjects had ventricular premature beats at rest, which in the case of 1 disappeared during work. Primary ST-T changes occurred in 3 cases at levels of energy expenditure of 1.8 to 2.8 calories per minute.

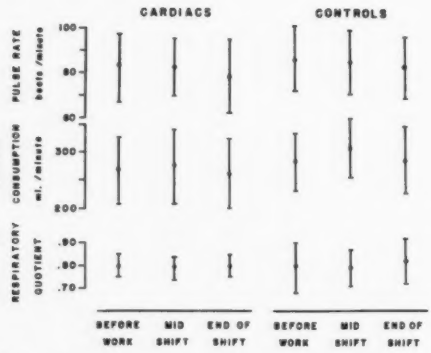


FIG. 9. Average resting pulse rate, oxygen consumption, and respiratory quotient for cardiac and control subjects at 3 points in the work shift. Dots represent averages, horizontal bars ± 1 S.D.

The electrocardiographic changes in cardiac and control groups were similar except for ventricular premature beats that appeared during work only in the cardiac group. The low incidence of ST-T changes at this level of work in these subjects is not surprising, since only 23 per cent had shown abnormal or borderline response to Master's exercise-tolerance test, which requires a larger expenditure of energy.

Fatigue

Objective evidence of fatigue was sought in our data. A sustained elevation of the resting oxygen consumption and of the resting pulse rate have been observed to follow strenuous exertion,[11, 12] suggesting that basal physiologic mechanisms have been unable to meet the current demands of the body. The respiratory quotient has likewise been noted to drop during prolonged exercise,[13] suggesting an exhaustion of the readily available carbohydrate stores of the body. Figure 9 summarizes the changes observed in these 3 parameters at rest at the beginning, middle and end of the work shift. Both cardiac and control subjects show a minor but not statistically significant elevation of oxygen consumption at midshifts, which may be attributed to the lunch or supper ingested by most of them just before the observations were made. Aside from this observation, there are no consistent changes in the resting oxygen consumption, pulse rate or respiratory quotient during the day in either cardiac or control group, and no significant differences between the 2 groups. Thus, as might be anticipated from the level of energy expenditure encountered, there is no evidence of fatigue in the over-all process of energy production. Other types of fatigue not measured by the methods of this study may, of course, have been present.

DISCUSSION

How representative were the jobs studied? Although not selected for statistical purposes, the jobs appeared typical of those held by a third of the total working population of a large industrial city and by a large percentage of working cardiac subjects studied at the Work Classification Clinic of the Cleveland Area Heart Society. The jobs ranged from menial to managerial and from sedentary to active, and were distributed throughout all departments of these 3 metal-manufacturing plants.

The energy cost of the type of work studied is remarkably low in relation to other human activities. A champion athlete can maintain an energy expenditure of 26.5 calories per minute for several minutes during a 2-mile run or skiing.[14, 15]

Taylor et al.[16] found that a group of healthy but untrained young men could achieve a maximum rate of energy expenditure of approximately 18 calories per minute on a treadmill. These rates are obviously unrealistic in relation to the requirements of daily work. Passmore and Durnin,[4] reasoning from their own data and those of German workers, conclude that 5 calories per minute during working hours "probably represents the upper rates of daily energy expenditure that can be maintained regularly in heavy industry." Garry et al.,[17] using methods similar to those of the present study, have found the average rate of energy expenditure by coal miners during the underground shift to be 4.3 calories per minute. In the same study, clerks at the mine had an average working rate of

7 calories per minute. In the present study, e average rate of energy expenditure was ore comparable to that of the clerks. During e working shift for the entire cardiac group e rate was 1.97 calories per minute, ranging om 1.54 calories per minute for the miscel- neous group (planning clerk, tool and laun- y crib attendant, etc.) to 2.35 calories per nute for the warehousemen (stock pickers). e energy requirements of these jobs there- re lie in the lower range of possible sus- ined-energy output. In fact, the workers ay expend energy at a higher rate on the b than off. This surprising conclusion is sed on the findings of Garry et al., that ring the 8 nonworking waking hours 1,400 lories, or 2.96 calories per minute, were ex- nded by coal miners and clerks, a rate which is higher than the average working rate for any of the groups in the present study. The low rates of energy expenditure at work are not attributable to heart disease as such, since no statistically significant difference in either average or maximum rate could be demonstrated when the cardiac subjects were compared with healthy men performing the same job. The subjects had not been downgraded to less difficult jobs because of the development of heart disease, according to the industrial physicians, consulting physicians and personnel managers.

Granted, then, that the energy demands of such factory work are not great, does the work nevertheless cause strain on the cardiovascular system of workers with heart disease? Certain individuals have been cited here who, in spite of the relatively light character of the work, developed heart rates of over 120 per minute or blood pressures of over 184 systolic or 90 diastolic, and electrocardiographic changes.

These physiologic alterations may have variable significance. When they occur singly and infrequently, as in the control group, they may be insignificant or secondary to obesity or benign essential hypertension. The concurrence of several abnormalities in the same subject is probably significant. Their occurrence in 2 subjects, who died unexpectedly within 4 months of the study, suggests encroachment upon a diminished cardiac reserve. It would be desirable, although not presently practicable, to monitor several parameters of cardiovascular function in the average cardiac patient at work. The Master 2-step test may be used to elicit such changes in the office or laboratory. It is important to recognize, however, that the Master step test calls for the expenditure of 8.5 calories per minute, a rate in excess of any peak observed in any of the workers studied. Certainly an individual with heart disease, who can make this exertion without developing excessive heart rate, blood pressure or abnormal electrocardiographic changes, would not be expected to show adverse effects during a job requiring average peaks of 3.45 calories per minute, or an average sustained effort of only 2 calories per minute. On the other hand, the cardiac patient who does show an abnormal step-test response may be able to perform safely at the rates of energy expenditure required by his job. The decision to return such an individual to work may be made in view of the fact that merely keeping him at home without further restriction probably will not reduce his energy below that required by work. The patient's work may, of course, entail other forms of stress than those measured in calories, but emotional and personal problems may be aggravated and are seldom solved by keeping a worker idle.

Summary

Sixty-two subjects, 36 with heart disease and 26 healthy controls, were observed during a normal working day in 3 metal-manufacturing plants. The workers are considered representative of at least a third of the working population of a large industrial city. Their average rate of energy expenditure during the shift was of the order of 2 calories per minute, a low rate and one comparable to that observed during nonworking activities. The maximum rate of energy expenditure rarely exceeded twice the resting rate. A few subjects with heart disease developed disorders of cardiovascular function in terms of blood pressure, heart rate or electrocardiogram dis-

orders that may have had serious prognostic significance. Energy expenditure correlated well with pulmonary ventilation, and poorly with pulse rate at the levels observed. No objective evidence of fatigue was detected.

Acknowledgment

The authors wish to express their gratitude to Richard Mackey, Herbert Medoff, James L. Phillips, Frank Tiberio, and Norman Zucker for invaluable assistance in collecting and preparing the data, to the volunteer subjects and personnel of the Cleveland Graphite Bronze Company Division of Clevite Corporation, Jack and Heintz, Inc., and Thompson Products, Inc., and to Dr. Arthur Littell and Mr. Melvin Conway for assistance in the statistical analysis.

Summario in Interlingua

Sexanta-duo subjectos—36 con morbo cardiac e 26 normales a titulo de controlo—esseva observate in 3 fabricas metallurgic durante un typic die de travalio. Es opinate que le subjectos seligite esseva representative de al minus un tertio del population travaliante de un grande citate industrial. Le expensa medie de energia in le curso del jornata esseva del ordine de 2 calorias per minuta. Iste valor es basse in comparation con observationes in activitates altere que travalio. Le intensitate del expensa de energia attingeva rarmente maximos de plus que duo vices le valor de reposo. Plure subjectos con morbo cardiac disveloppava disordines del functiones cardiovascular—tanto in le pression de sanguine e le frequentia cardiac como etiam in le manifestationes electrocardiographic—le quales es possibilemente de serie signification prognostic. Le expensa de energia se monstrava ben correlationate con le ventilation pulmonar, sed illo se trovara pauco correlationate con le frequentia del pulso a omne le nivellos studiate. Nulle signos objective de fatiga esseva detegite.

REFERENCES

1. Hellerstein, H. K., and Ford, A. B.: The rehabilitation of the cardiac patient. J.A.M.A. **164**: 226, 1957.
2. Ford, A. B., and Hellerstein, H. K.: The energy cost of the Master two-step test. J.A.M.A. **164**: 1868, 1957.
3. Bruce, R. A., Lovejoy, F. W., Yu, P. N. G., and McDowell, M.: Evaluation and significance of physical fitness for moderate work; study of patients with cardiovascular or pulmonary diseases. Arch. Indust. Hyg. **4**: 236, 1951.
4. Passmore, R., and Durnin, J. V. G. A.: Human energy expenditure. Physiol. Rev. **35**: 801, 1955.
5. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Blood Vessels. Ed. 5. New York Heart Association, 1953.
6. Occupational Inventory of the Number and Kinds of Jobs in Cuyahoga County, 1940. The Occupational Planning Committee of the Welfare Federation of Cleveland, 1947.
7. Müller, E. A., and Franz, H.: Energieverbrauchsmessungen bei beruflicher Arbeit mit einer Verbesserten Respirations—Gasuhr. Arbeitsphysiologie **14**: 499, 1952.
8. Scholander, P. F.: Analyzer for accurate estimation of respiratory gases in one-half cubic centimeter samples. J. Biol. Chem. **167**: 235, 1947.
9. Cathcart, E. P., and Cuthbertson, D. P.: The composition and distribution of the fatty substances of the human subject. J. Physiol. **72**: 349, 1931.
10. Lundgren, N. P. V.: The physiological effects of time schedule work on lumber-workers. Acta physiol. scandinav. **13**: Suppl. 41, 1946.
11. Hill, A. V., Long, C. N. H., and Lupton, H.: Muscular exercise, lactic acid and the supply and utilization of oxygen. Proc. Roy. Soc. London, Series B, **97**: 84, 1925.
12. Brouha, L.: Fatigue—Measuring and reducing it. Advanced Management **19**: 9, 1954.
13. Courtice, F. C., and Douglas, C. G.: The effects of prolonged muscular exercise on the metabolism. Proc. Roy. Soc. London, Series B, **119**: 381, 1935.
14. Christensen, E. H., and Hogberg, P.: Physiology of skiing. Arbeitsphysiologie **14**: 292, 1950.
15. Robinson, S., Edwards, H. T., and Dill, D. B.: New records in human power. Science **85**: 409, 1937.
16. Taylor, H. L., Buskirk, E., and Henschel, A.: Maximal oxygen intake as an objective measure of cardio-respiratory performance. J. Appl. Physiol. **8**: 73, 1955.
17. Garry, R. C., Passmore, R., Warnock, G. M., and Durnin, J. V. G. A.: Studies on expenditure of energy and consumption of food by miners and clerks, Fife, Scotland, 1952. Medical Research Council special Report Series No. 289, London, HMS Stationery Office, 1955.

Ventricular Septal Defect in Infants and Children

A Correlation of Clinical, Physiologic, and Autopsy Data

By DONALD C. FYLER, M.D., ABRAHAM M. RUDOLPH, M.D., MARTIN H. WITTENBORG, M.D., AND ALEXANDER S. NADAS, M.D.

Now that ventricular septal defect is amenable to surgical repair it is most important to define the indications for surgical intervention. In this paper the natural history of the disease and its clinical and physiologic characteristics are carefully detailed. These observations permit better recognition and understanding of the condition and offer a basis for comparison with results after surgery.

IT HAS BEEN demonstrated recently that ventricular septal defects in children can be repaired surgically with an acceptable mortality rate under appropriate circumstances.[1-3] For infants who at present are not considered suitable candidates for direct surgical repair, an ingenious palliative operation offers considerable theoretical promise.[4] To achieve a better understanding of the nature of the anomaly and to arrive at some working hypothesis in regard to operative indications, we reviewed the clinical picture, the physiologic data, and the natural history of our patients with proven ventricular septal defect.

MATERIALS AND METHODS

The physiological data were surveyed on all patients admitted to the Children's Medical Center, Boston, between 1950 and 1956 and diagnosed at cardiac catheterization as having a ventricular septal defect. All these subjects had an increase in oxygen content of at least a 1.0 volume per cent at the right ventricular level as compared to the right atrial sample. The catheterized patients were considered to have severe disease on clinical grounds; thus they represent a select group from the total number of children with ventricular septal defect attending our clinic.

The catheterization data were reviewed for completeness and all patients with associated cardiac anomalies other than pulmonary stenosis or aortic regurgitation were arbitrarily excluded. Cases of ventricular septal defect and pulmonary stenosis with a resting arterial saturation of less than 94 per cent were also eliminated as examples of the tetralogy of Fallot.* The remaining 98 patients form the basis of the present report.

All patients were studied with 7-foot radiograms and fluoroscopy. All had at least one 12-lead electrocardiogram that was classified in regard to ventricular hypertrophy. Phonocardiographic observations were made on about one quarter of the patients by means of a Sanborn Stetho-Cardiette or Twin-Beam apparatus.

Cardiac catheterization was carried out under sedation either with opiates or a combination of Demerol, Phenergan, and Thorazine. The catheters used were Cournand or Lehman no. 5 or no. 6. Pressure measurements were obtained with Sanborn electromanometers or Statham P-23-D strain-gage manometers. A Sanborn Polyviso recording apparatus was used. Blood oxygen determinations were made by the Van Slyke or spectrophotometric technics.[5] Oxygen consumption was determined, when possible, by collection of expired air samples in a Douglas bag and analysis by means of a Tissot spirometer and a Pauling oxygen analyzer; in the others it was estimated on the basis of 180 ml./min./M^2. Zero level for pressure was assumed to be at one half the anteroposterior diameter of the chest. Pulmonary venous oxygen saturation was assumed in all instances to be 98 per cent of capacity. (We are fully aware that the calculation of shunts derived on the basis of this figure may be of questionable accuracy in some instances, particularly in infants.)

In order to simplify the evaluation of the case material, certain arbitrary definitions were made. Pulmonary stenosis was considered to be present when a systolic gradient of at least 25 mm. Hg existed between right ventricle and pulmonary artery. Pulmonary vascular resistance was cal-

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*One small infant with ventricular defect and pulmonary stenosis, a large left-to-right shunt, and resting arterial saturation of 93 per cent was not excluded, since slight pulmonary venous unsaturation at cardiac catheterization is not uncommon in small infants.

TABLE 1.—*Physiologic Classification of 98 Patients with Ventricular Septal Defect*

Uncomplicated	Complicated
Left-to-right shunt	Left-to-right shunt
Small 18	Pulmonary stenosis 20
Large 24	Pulmonary vascular obstruction 36*

*Includes 2 patients with pulmonary stenosis and pulmonary vascular obstruction.

culated in terms of mm. Hg pressure gradient across the pulmonary vascular bed per liter of pulmonary blood flow per square meter of body surface area per minute and expressed as units of pulmonary resistance.[6] The upper limit of normal was defined as 3.0 units (240 dyne-sec.-cm.$^{-5}$). Since our physiologic data were accumulated under varying circumstances and since shunt calculations by the Fick principle are subject to a not inconsiderable error, our left-to-right shunts were divided into those with pulmonary flow more than twice systemic flow and those with a lower ratio. The pitfalls of pulmonary flow calculations are such that the larger flows are subject to increasing errors that reach dramatic proportions with the largest of left-to-right shunts. The smaller flows (pulmonary flow less than twice systemic flow) probably represent accurate estimations.

We have classified the entire group physiolgically into 4 subdivisions on the basis of (a) size of uncomplicated left-to-right shunt (small or large), or (b) presence of complications (pulmonary vascular obstruction or pulmonary stenosis) (table 1). In contrast to other studies[7-9] we will not discuss these variants under separate headings, since their clinical and physiologic features blended into one another. We prefer to consider the group as a whole, pointing out the variations in relation to the physiologic subdivisions as seems indicated.

The average age of the patients at the time of cardiac catheterization was 5.9 years. Six were over the age of 12, and 20 were under the age of 2 years. There were 50 females and 48 males in the group, but there were almost twice as many girls as boys with pulmonary vascular obstruction.*

*It is also worth pointing out that pulmonary vascular obstruction was not any more common in the older children than in the infant group. The 36 individuals with pulmonary vascular obstruction were divided in the following manner: 8 of 20 infants, 26 of 72 children between 2 and 12 years, and 2 out of 6 individuals over 12 years of age.

In addition to the 98 patients with complete clinical and physiologic studies, we also included in this report 5 patients with uncomplicated ventricular septal defect in whom complete autopsy data are available. These children will only be discussed in terms of course and prognosis since the clinical data available on them are incomplete.

OBSERVATIONS

History

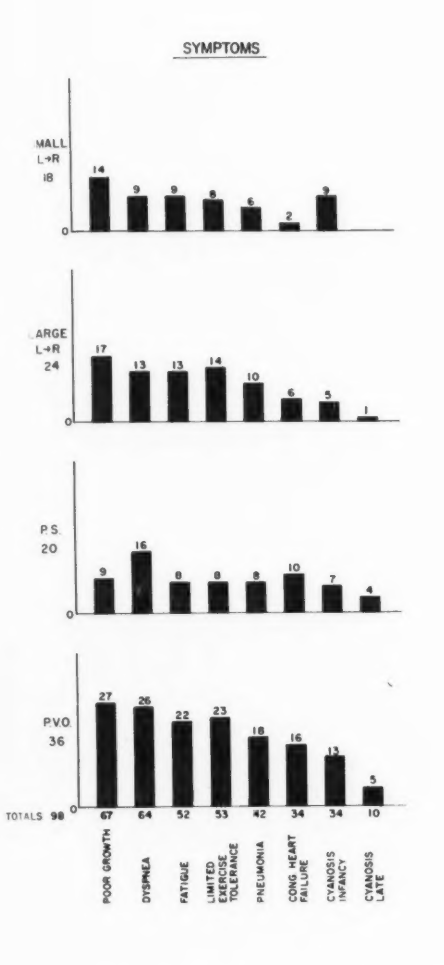
Discovery of Heart Disease. In the majority, heart disease was diagnosed on the basis of the discovery of a murmur in infancy. Fifty-seven children had a murmur noted at the age of 3 months or earlier, but only 15 of these were reported to have been present "at birth." Twelve patients were first noted to have a murmur after the age of 1 year. The time of discovery of heart disease was independent of the size of left-to-right shunt, the presence or absence of pulmonary stenosis or pulmonary vascular obstruction.

Of 85 cases with sufficient information, 45 were found to have heart disease on routine or chance examination, whereas 40 were seen by a physician because of symptoms referable to heart disease.

Symptoms. By and large, symptomatology was most marked in early infancy; of the 52 patients with severe symptoms, 43 were less than 1 year of age. The correlation of symptomatology with the basic physiologic information is presented in figure 1. Poor growth was reported by the parents in about two thirds of this series. Contrariwise, specifically recorded "good" growth was unusual and of the 19 instances in which it occurred, 7 were patients with pulmonary stenosis.

One or more episodes of congestive failure appeared in the history of 34 patients; in many small infants this diagnosis was confused by the presence of pneumonia.

A vague history of intermittent, mild cyanosis with respiratory difficulty or with crying, disappearing after the first few weeks of life, was obtained in 34 patients. Indeed, 4 patients were initially examined in the neonatal period because of cyanosis. This symptom was surprisingly common among the children with uncomplicated small left-to-right shunts.



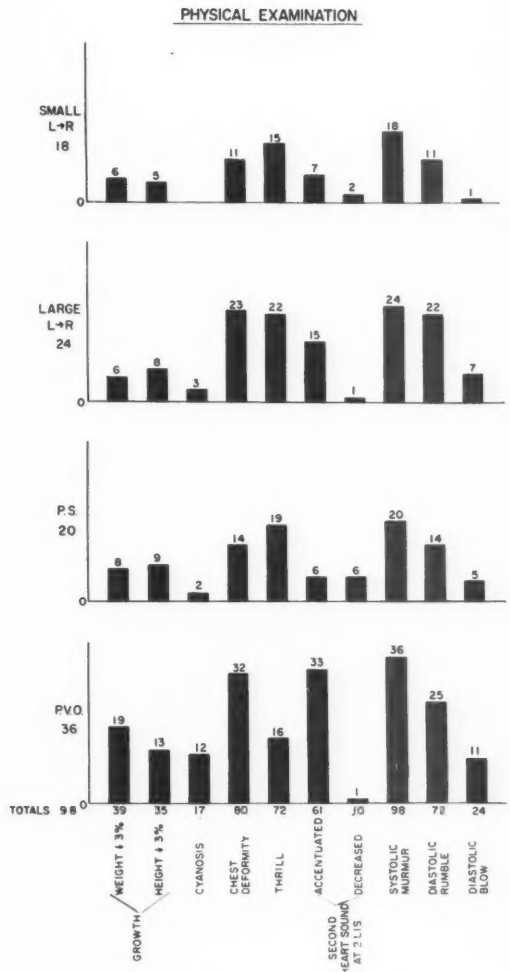


FIG. 1 *Left.* Symptoms related to physiologic classification. L→R, left-to-right shunt.
FIG. 2 *Right.* Physical examination related to physiologic classification. 2LIS, second left intercostal space.

Ten patients gave a history of late appearance of mild cyanosis on exercise; 9 of these had either associated pulmonary stenosis or elevated pulmonary vascular resistance.

The following other problems appeared in the histories of some patients: squatting 7 (uncomplicated left-to-right shunt 3, pulmonary vascular obstruction 3, pulmonary stenosis 1); paroxysmal tachycardia 5; subacute bacterial endocarditis 3 (aortic regurgitation 2); hemoptysis 2; acute rheumatic fever 1; chest pain 1; and mongolism 1.

Physical Examination

The salient features of the physical examination as recorded during the admission for cardiac catheterization are presented in figure 2, and the associated anomalies are listed in table 2. Of 98 patients more than one third were markedly underweight, falling below the third percentile on our standard growth charts; 70 were below the twenty-fifth percentile. Height measurements were proportional to weight measurements. The poorest growth was noted in patients with elevated

TABLE 2.—*Associated Anomalies*

Anomaly*	Physiologic classification
Mental retardation	Pulmonary vascular obstruction
Mental retardation	Pulmonary vascular obstruction
Club foot	Pulmonary vascular obstruction
Mongolism	Pulmonary vascular obstruction
Strabismus	Pulmonary vascular obstruction
Psychomotor seizures	Pulmonary stenosis
Hypoplasia of testes and abnormal teeth	Pulmonary stenosis
Scoliosis and webbed neck	Large left-to-right shunt
Abnormal vertebrae	Small left-to-right shunt
Coloboma	Small left-to-right shunt

*Each anomaly represents 1 patient. Note frequent occurrence of pulmonary vascular obstruction.

pulmonary vascular resistance; only 3 patients in this group were above the twenty-fifth percentile for weight.

Cyanosis was suspected clinically in 17 patients, 11 of whom had in fact arterial oxygen saturation below 94 per cent at catheterization (table 3). An additional 13 patients had clinically unsuspected arterial unsaturation.

The chest was considered asymmetrical or deformed in anteroposterior diameter in 80 patients. The presence of a large shunt was almost invariably associated with prominence of the left chest; patients who had no chest deformity tended to have small hearts by x-ray.

All infants under the age of 2 years showed a right ventricular impulse alone, or in combination with a left ventricular impulse. A purely apical impulse was often associated with electrocardiographic evidence of left ventricular hypertrophy or with a normal electrocardiogram. The correlation of right ventricular hypertrophy with a xiphoid impulse was not striking. Almost all patients with a pure xiphoid impulse, however, had a right ventricular systolic pressure of over 45 mm. Hg.

A thrill was noted in 72 patients. It was usually present in the group of uncomplicated

TABLE 3.—*Relationship of Clinical Cyanosis to Arterial Saturation in the Four Physiologic Subgroups*

	Numbers of Patients	Arterial saturation less than 94%			
		Clinically cyanotic		Clinically acyanotic	
Small left-to-right	18	0	0	1	18
Large left-to-right	24	3	2	0	21
Pulmonary stenosis	20	2	0	1	18
Pulmonary vascular obstruction	36	12	9	11	24
			11	13	
Total	98	17	24		81

left-to-right shunts and in those who had associated pulmonary stenosis. By contrast, less than one half of the patients with increased pulmonary resistance showed a thrill.

The first heart sound was not uniformly commented upon, but we have the distinct impression that it was masked by the loud systolic murmur at the lower left sternal border in a high percentage of cases.

A third heart sound was heard in 51 patients and was associated with a low-frequency diastolic murmur at the apex or lower left sternal border in all but 2 instances.

The second heart sound at the second left intercostal space was analyzed most carefully, both in regard to splitting and intensity. A split second sound was found in all but 12 individuals; one half of these had pulmonary vascular obstruction. The second heart sound was obscured in 4 of the 5 patients with aortic regurgitation.

The intensity of the second sound at the pulmonary area correlated fairly well with the mean pulmonary artery pressure (table 4). Decreased intensity of the second heart sound was associated with a mean pulmonary artery pressure of less than 30 mm. Hg in all but 1 infant. Increased intensity of the second heart sound was not quite so specific, still almost 80 per cent of the patients with increased second sound at the second left interspace had a mean pulmonary pressure over 30 mm. Hg.

Systolic Murmur. A blowing, holosystolic murmur was present in every case of this se-

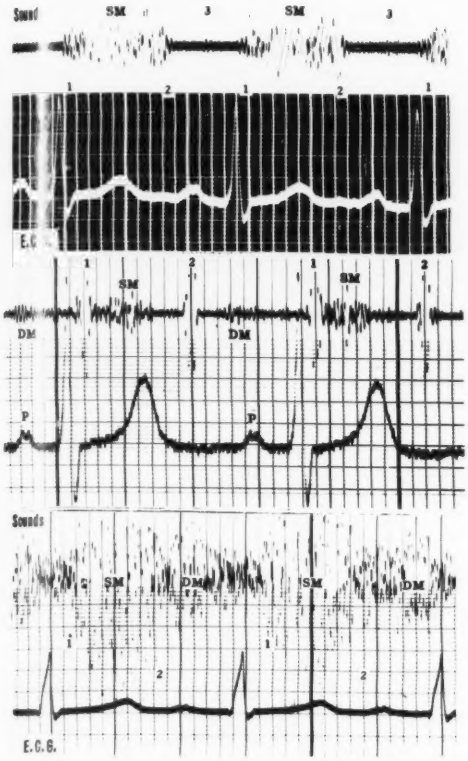


Fig. 3 *Top.* Phonocardiogram taken at the lower left sternal border in patient with ventricular defect. Note the high intensity, medium frequency, holosystolic murmur (SM). 1, first sound; 2, second sound; 3, third sound.

Fig. 4 *Middle.* Phonocardiogram at apex of patient with ventricular defect. Note the lower intensity systolic murmur and the low-frequency middiastolic murmur (DM).

Fig. 5 *Bottom.* Phonocardiogram at mid-left sternal border of patient with ventricular defect, aortic regurgitation, and mild pulmonary stenosis. Note the high-frequency and intensity diamond-shaped systolic murmur (SM) and crescendo-decrescendo diastolic murmur (DM).

ric (fig. 3); in 82 the murmur was maximal at he mid- or lower left sternal border. Of th 8 patients recorded as having a systolic mu mur maximal at the upper sternal border, 5 l d associated pulmonary stenosis. Of the 8 pa ents with an apical murmur, 7 had pulmo ary vascular obstruction. As may be seen fro table 5, murmurs of lesser intensity were

TABLE 4.—*Intensity of Second Heart Sound Related to Mean Pulmonary Arterial Pressure*

		Mean P.A. pressure					
		Below 30 mm. Hg			Over 30 mm. Hg		
Intensity of second heart sound at the pulmonary area		↓	N	↑	↓	N	↑
Small left-to-right	(18)	2	9	7			
Large left-to-right	(21)	1	5	2			13
Pulmonary stenosis	(19)*	5	4	4		3	3
Pulmonary vascular obstruction	(36)				1†	3	32

*Second heart sound obscured by murmur.
†Infant.

TABLE 5.—*Intensity of Systolic Murmur Related to Physiologic Classification*

Defect		Intensity of systolic murmur Grades 2-3	Grades 4-6
Small left-to-right shunt	18	4	14
Large left-to-right shunt	24	6	18
Pulmonary stenosis	20	2	18
Pulmonary vascular obstruction	36	22	14
Total	98	34	64

rather common in the group with pulmonary vascular obstruction, but relatively rare in all the other subdivisions.

Diastolic Rumbling Murmurs. A low frequency, low to moderate intensity, middiastolic or presystolic murmur maximal at the apex or lower left sternal border was present in 72 patients (fig. 4). These murmurs usually began with the third sound and were quite short in duration. Whether they appeared in middiastole or presystole seemed to depend principally on the heart rate.

As seen in figure 2, a large proportion of all 4 physiologic groups had low-frequency diastolic murmurs, but the pure, large left-to-right shunts had this murmur almost without exception.

In table 6 the heart size and the size of the shunt are related to the presence or absence of a diastolic rumbling murmur. If a patient with a ventricular septal defect had an apical diastolic rumble, it was very likely that he would have appreciable cardiac enlargement,

TABLE 6.—*Relation of Presence or Absence of Diastolic Rumble to Heart Size and Shunt Size*

	Present (%)	Absent (%)
Heart size one plus or less	14 (19)	12 (48)
Heart size two to four plus	59 (81)	13 (52)
Totals	73 (100)	25 (100)
Small left-to-right shunt*	35 (50)	18 (72)
Large left-to-right shunt	35 (50)	7 (28)
Totals	70 (100)	25 (100)

*No shunt calculated in 3.

but not necessarily a large shunt. Conversely, absence of a diastolic rumble meant that the patient probably had only a small left-to-right shunt, but may or may not have had significant cardiac enlargement.

Diastolic Blowing Murmurs. A protodiastolic, high-frequency, blowing murmur of high intensity was heard along the left sternal border in 24 patients (fig. 5). These murmurs were associated with an elevated mean pulmonary artery pressure (over 40 mm. Hg) in all but 9 patients; 4 of the latter group had clear-cut aortic regurgitation.

Electrocardiogram

Of the total of 267 electrocardiograms available, those taken during admission for cardiac catheterization were used for detailed analysis (fig. 6). The others were evaluated only for changes through the years.

Axis Deviation. Left axis deviation (0 to −30°) was uncommon, appearing only 9 times in the entire group. Two of these children had otherwise normal tracings, 1 (a child with pulmonary stenosis) had pure right ventricular hypertrophy, and in the others left ventricular hypertrophy alone or in combination with right ventricular hypertrophy was present.

By contrast, right axis deviation (+90 to +180°) was common, appearing 31 times in the entire series. In 29 tracings there was right ventricular hypertrophy alone or in combination with left ventricular hypertrophy. One patient with a large uncomplicated left-to-right shunt showed right axis deviation and pure left ventricular hypertrophy; another showed no evidence of ventricular hypertrophy.

Normal axis deviation (0 to +90°) was present in well over one half the total series and bore no specific relationship to the various ventricular hypertrophy patterns. Indeterminate axis was uncommon and likewise bore no relationship to the patterns of ventricular hypertrophy.

Incomplete Right Bundle-Branch Block. An rSr′ or rsR′ pattern in the right chest leads with a ventricular activation time of at least 0.04 second was found in 54 cases. No definite relationship could be established between this finding and evidence of right, left, and combined ventricular hypertrophy.

P Pulmonale. A P wave of at least 2.5 mm. in height with a "peaked" contour in the right precordial leads or in lead II was found in 17 patients. Fourteen of these had either associated pulmonary vascular obstruction or pulmonary stenosis. Six had arterial oxygen saturations of less than 94 per cent, all with pulmonary vascular obstruction. There was no correlation between the right atrial mean pressure and the presence of P pulmonale.

P Mitrale. Notched or flat-topped P waves in the standard leads I and II or in the left precordial leads were found in 11 patients. In all but 1 there was left ventricular dominance or hypertrophy alone or in combination with right ventricular hypertrophy. Satisfactory mean pulmonary wedge pressures, obtained in 5 of these 11 patients, ranged from 11 to 17 mm. Hg. There was no correlation between the presence of P mitrale and the right atrial mean pressure.

Combined Atrial Hypertrophy. An abnormally broad and tall P wave in any of the standard or precordial leads was found in 6 patients. Five of these had pulmonary vascular obstruction.

Prolonged P-R Interval. An abnormally long P-R interval for heart rate and age, according to our tables of normal subjects,[8] was seen only 11 times in the entire series and was not associated with any particular physiologic subgroup.

S-T and T-Wave Changes. Significant de-

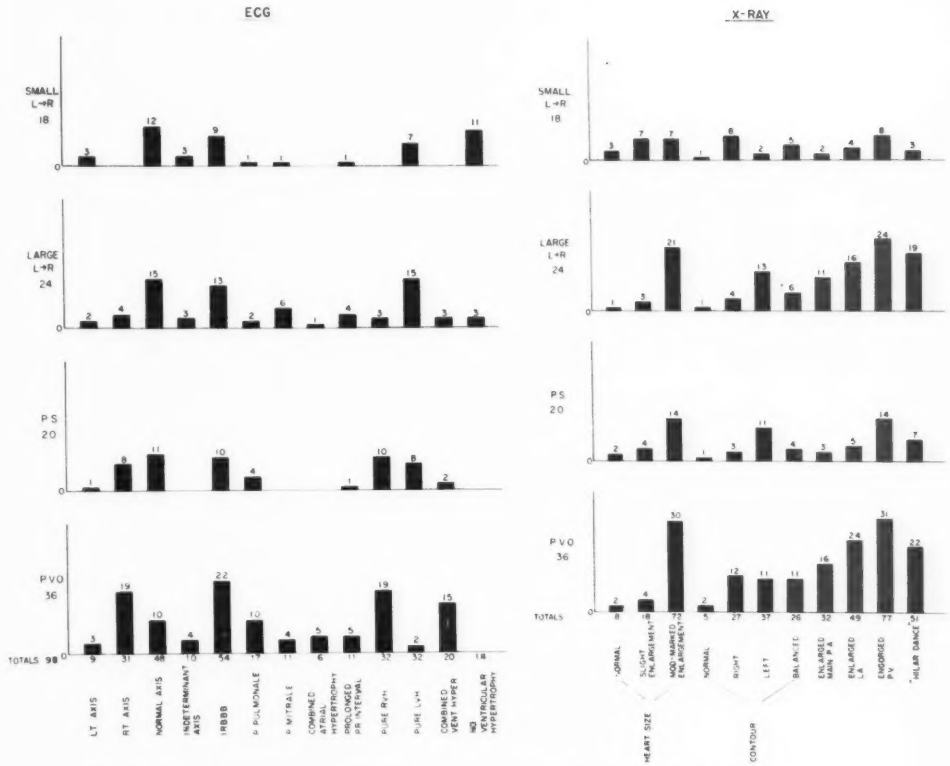


FIG. 6 *Left.* Electrocardiogram related to physiologic classification. IRBB, incomplete right bundle-branch block; RVH, right ventricular hypertrophy; LVH, left ventricular hypertrophy.

FIG. 7 *Right.* X-rays related to physiologic classification. PA, pulmonary artery; LA, left atrium; PV, pulmonary vasculature.

pression of the S-T segment and inversion of the T wave in the left precordial leads ("strain-pattern") was observed in 7 cases. Five of these had aortic regurgitation and 2 had uncomplicated large left-to-right shunts.

Because of the difficulties in interpreting degrees of right precordial T-wave inversion in infants and small children, no attempt was made to determine the incidence of "right strain pattern."

Ventricular Hypertrophy. Pure right ventricular hypertrophy was seen in 32 patients, almost all individuals with pulmonary stenosis or vascular obstruction. Of the 3 patients with pure right ventricular hypertrophy who had large uncomplicated left-to-right shunts, one had a functionally single ventricle, another was still an infant when last observed, and the third had borderline infundibular pulmonary stenosis (gradient 23 mm. Hg). No patient with an uncomplicated small shunt had pure right ventricular hypertrophy.

Pure left ventricular hypertrophy was present in 32 children; most of these fell into the uncomplicated left-to-right shunt group but a few had associated pulmonary stenosis. Surprisingly enough, 2 patients with pure left ventricular hypertrophy had pulmonary vascular obstruction; one was still an infant when last observed and the other had only minimal elevation of pulmonary vascular resistance (4.0 units).

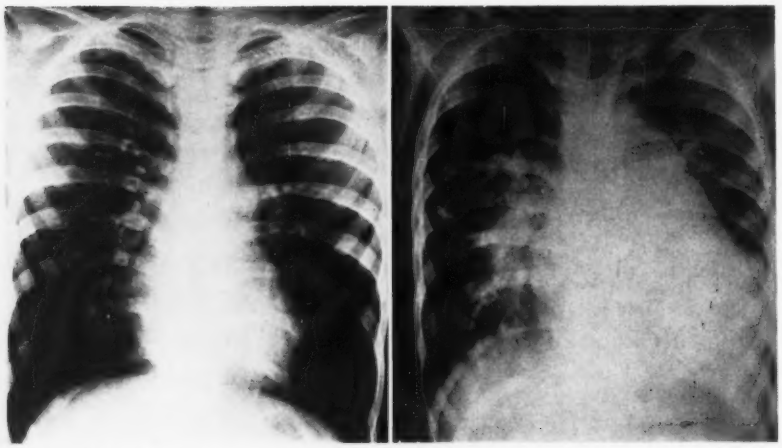


FIG. 8 *Left.* Relatively normal cardiac contour in patient with pulmonary vascular obstruction.

FIG. 9 *Right.* Grossly abnormal cardiac silhouette in another patient with pulmonary vascular obstruction.

Combined ventricular hypertrophy was seen in 20 patients, most of them with pulmonary vascular obstruction.

There were 14 patients who showed no evidence of ventricular hypertrophy. These electrocardiograms were found only in the uncomplicated left-to-right shunt groups.

X-Ray

The x-ray and fluoroscopic studies performed during admission for cardiac catheterization were analyzed in detail (fig. 7); the other available films were used to determine changes over the years and will be discussed in the section on course and prognosis.

Heart Size. It may be seen that most patients had moderate or marked cardiac enlargement; as pointed out earlier, this was a group selected for cardiac catheterization on account of severe disease. It is interesting that patients with small uncomplicated left-to-right shunts may on occasion have significant cardiac enlargement. Contrariwise, individuals with pulmonary vascular obstruction and large left-to-right shunts may have only relatively small hearts under exceptional circumstances. When the heart size was correlated with a prior history of congestive heart failure or pneumonia, it appeared that patients with such a past history were more likely to have definite cardiac enlargement. However, the presence of cardiomegaly could not be taken as evidence for pre-existing congestive failure or pneumonia (table 7).

TABLE 7.—*Heart Size Related to History of Congestive Heart Failure*

Clinical features	Heart size		Total
	Slightly enlarged	Markedly enlarged	
History of congestive heart failure	5	32	37
No history of congestive heart failure	21	40	61
History of pneumonia	10	34	44
No history of pneumonia	16	38	54
Totals	26	72	98

Cardiac Contour. It may be seen from figure 7 that the radiologic interpretation of ventricular enlargement was not particularly helpful in attempting to distinguish the physiologic groups. A normal contour was discernible in 2 patients with marked vascular obstruction, and pure right ventricular enlargement was thought to be present in 8 individuals with small shunts. Figures 8 and 9 show the extreme difference noted in patients with marked pulmonary vascular obstruction.

TABLE 8.—*General Survey of Physiologic Data*

Anomaly		Small left-to-right shunt	Large left-to-right shunt	Pulmonary stenosis	Pulmonary vascular obstruction	Pulmonary stenosis and pulmonary vascular obstruction	Mean pulmonary arterial pressure >30 mm. Hg	Shunt not calculated
Total small left-to-right	53	18	..	7	26	2	30	3*
Total large left-to-right	42	..	24	13	5	..	25	..
Total pulmonary stenosis	22	9	13	22	2	2	8	..
Total pulmonary vascular obstruction	36	28	5	2	36	2	36	..
Total aortic regurgitation	5	0	5	1	1	0	1	

*All severe pulmonary vascular obstruction.

No close correlation between electrocardiographic ventricular hypertrophy and ventricular enlargement as determined by x-ray could be found; nor was it possible to establish a relationship between the right ventricular systolic pressure and the ventricular contour at x-ray.

Main Pulmonary Artery Segment. A significantly enlarged main pulmonary artery segment seemed to indicate that the patient had either pulmonary vascular obstruction or a large left-to-right shunt, but only 3 of the patients with pulmonary stenosis showed enlargement of the main pulmonary artery segment. The pulmonary artery segment was large in one half of the patients with pulmonary artery mean pressure above 40 mm. Hg and was of normal size in the majority of patients with mean pressures below this figure.

Left Atrial Enlargement. Left atrial enlargement was present in three fourths of the children with large uncomplicated left-to-right shunts or pulmonary vascular obstruction, but it was not unusual in the other groups either. There was no clear-cut correlation between the size of the left atrium and the size of the left-to-right shunt.

Pulmonary Vasculature. The average diameter of the pulmonary vessels in the middle third of the lung fields was considered to be greater than normal in 77 individuals. Every patient with a large, uncomplicated left-to-right shunt had this finding but it was present also in about one half of the cases with small, uncomplicated shunts. Three quarters of our group with associated pulmonary stenosis and 90 per cent of the children with pulmonary vascular obstruction also had engorged pulmonary vessels.

In 4 patients, all with pulmonary vascular obstruction, there was pulmonary vascular engorgement in the middle third of the lung fields with relative ischemia in the periphery.

Two children with pulmonary vascular obstruction showed asymmetrical pulmonary vasculature and in both instances the vessels were decreased in prominence on the left and increased (with unilateral "hilar dance") on the right.

Expansile Pulsations. Expansile pulsations were noted in over 50 per cent of the patients in this series and, though it was not seen in every child with pulmonary vascular engorgement, the incidence of "hilar dance" was proportional to the evidence of engorged pulmonary vessels.

Right Aortic Arch. A right aortic arch was present in 5 patients. Four of these had associated pulmonary stenosis, but 1 patient with a small uncomplicated left-to-right shunt also had a right aortic arch.

Catheterization Data

Table 8 presents a *general* survey of the physiologic data. Included in the total are, for instance, *all* patients with small shunts

TABLE 9.—*A-H. Detailed Physiologic Data*

Blood oxygen and pressure measurements	Small left-to-right shunt	Large left-to-right shunt	Pulmonary stenosis	Pulmonary vascular obstruction
Arteriovenous oxygen difference (vol. %)				
Pulmonary (PV*-PA)				
Under 1.0	0	8	2	0
Over 3.0	4	0	0	11
Average	2.8	1.2	1.7	2.9
No. of cases	18	24	20	36
Systemic (BA-RA)				
Under 3.0	1	4	2	3
Over 4.5	4	4	5	12
Average	3.9	3.8	3.7	4.3
No. of cases	18	24	20	33
Mean right atrial pressure				
Over 10 mm. Hg	0	1	0	3
Average	4.7	4.7	5.4	4.6
No. of cases	15	19	18	33
Mean pulmonary capillary wedge pressure				
Over 15 mm. Hg	2	4	3	0
Average	8.7	4.7	11.2	9.5
No. of cases	12	12	19	15
Mean pulmonary artery pressure				
Under 20 mm. Hg	6	2	8	0
Over 40 mm. Hg	0	8	6	33
Average	20	36	25	60
No. of cases	18	24	20	36
Pulmonary artery pressure				
Average systolic pressure	11	3	8	2
Average diastolic pressure	0	3	3	19
Average pulse pressure	17	30	23	39
No. of cases	18	24	20	36
Brachial artery pressure				
Average systolic pressure	105	103	109	97
Average diastolic pressure	63	59	63	60
Average pulse pressure	42	44	46	37
No. of cases†	15	22	20	33

TABLE 9.—*(Continued)*

Blood oxygen and pressure measurements	Small left-to-right shunt	Large left-to-right shunt	Pulmonary stenosis	Pulmonary vascular obstruction
Systolic gradient (BA-RV)				
Under 20 mm. Hg	0	4	8	2
Over 40 mm. Hg	15	13	5	
Average	69	44	26	1
No. of cases	15	22	18	3
Per cent brachial artery saturation				
Under 94	1	2	1‡	2
Under 93	0	1	0	1
Under 90	0	1	0	0
No. of cases	18	24	20	33

*Assumed to be 98% capacity.

†Five patients with aortic regurgitation not included.

‡Infant under age 6 months.

BA, brachial artery; PA, pulmonary artery; PV, pulmonary vein; RA, right atrium; RV, right ventricle.

including those with pulmonary stenosis and vascular obstruction as well.

For the purposes of this study, a left-to-right shunt producing a pulmonary flow twice the size of the systemic flow was taken as the dividing line between a large and a small shunt. There were 10 patients with calculated shunts of very large size; subject to previously noted errors, these shunts produced a pulmonary flow 4 to 5 times the systemic flow (pulmonary atrioventricular difference of less than 1.0 volume per cent) (table 9).

Pulmonary stenosis, in this series, was arbitrarily defined as a systolic pressure gradient between right ventricle and pulmonary artery of 25 mm. Hg or more. A right ventricular-pulmonary artery gradient occurred in association with small and large left-to-right shunts but no correlation could be found between the size of the shunt and the severity of the gradient. The interesting combination of pulmonary stenosis with increased pulmonary vascular resistance was observed twice. On the basis of continuous pressure tracing obtained during withdrawal of the

TABLE 10.—*Total Autopsy Material on Ventricular Defect from the Pathology Department, Children's Medical Center, 1950-1956*

Age (yr.)	Size ventricular septal defect (cm.)	Diameter of aortic valve (cm.)	Associated anomalies	Cause of death
2/12	0.4 x 0.2	0.7	Marked pulmonary vascular changes	Pneumonia
1/12	0.4 x 0.2	0.7	Bicuspid pulmonary valve, aortic incompetence, patent ductus arteriosus (0.7 cm. diameter)	Pneumonia
8/12	1.0	0.95	Mongolism, patent ductus arteriosus (0.2 cm. diameter)	Pneumonia, congestive heart failure
3/12	0.8 x 0.8	0.8	Mitral and tricuspid incompetency with fibroelastosis of these valves	Congestive heart failure, mycotic pneumonia
5/12	0.2 x 0.1	0.9	None	Pneumonia
23/12	0.8	1.4	Marked pulmonary vascular changes	Cardiac catheterization
13	2.0	2.5	Aortic regurgitation	Congestive heart failure, exploratory thoracotomy
5	2.2 x 1.8 muscular defect	1.4	Bicuspid aortic valve	Pneumonia, congestive heart failure

*Autopsy at the Massachusetts General Hospital, Boston.

catheter from the pulmonary artery, 6 patients were thought to have pure infundibular stenosis, 5 pure valvular stenosis, and 6 combined stenosis. There was definite correlation between the appearance of the pulmonary artery segment at x-ray, the site of maximal intensity of the murmur, and the site of stenosis as judged by cardiac catheterization.

Of the 36 patients with pulmonary vascular obstruction one third had a resistance over 9.0 units (720 dyne-sec.-cm.$^{-5}$) and one third had a resistance between 3.0 to 6.0 units. The error in these calculations is, of course, proportional to the error in calculating shunt size and estimating pulmonary wedge pressure.

Course of the Catheter. The right atrium, right ventricle, and pulmonary artery were entered in every case. The catheter was passed directly into the aorta in 6 children, into the left atrium via the atrial septum 4 times, and directly into the left ventricle via a ventricular septal defect 5 times.

Oxygen Consumption. Oxygen consumption was measured directly in 50 patients with an average oxygen consumption of 189 ml./min./M.^{2}

Blood Oxygen and Pressure Measurements. Table 9 presents the detailed physiologic observations. As expected, the individuals with uncomplicated large left-to-right shunts and those with pulmonary stenosis, most of whom

TABLE 11.—*Progression of Symptoms in 95 Cases (3 Dead)*

	Severe symptoms						Mild symptoms					
	Small L-to-R	Large L-to-R	PS*	PVO†	Total		Total	Small L-to-R	Large L-to-R	PS*	PVO†	
Infancy	3	13	12	15	43		52	15	10	8	19	Infancy 52
Same	1	10	8	9	37	←		0	7	1	1	Worse 9
Better	2	3	4	6		→	58	15	3	7	18	Same 43
Status last seen	1	17	9	10	37		58	17	6	11	24	Status last seen

*Pulmonary stenosis.

†Pulmonary vascular obstruction.

TABLE 12.—*Changing Growth Pattern of 32 Children with Ventricular Defect (Weight)**

	Under 3%	3 to 10%	10% and over	Total
Under age 1 year	18	10	4	32
Improved	4	5	0	9
Deteriorated		1		1
Over age 2 years	15	4	13	32

*First examined under age 1 year and followed for 2 years or longer.

Based on Stuart, H. C., anthropometric chart, The Children's Medical Center, Boston, Mass.

TABLE 13.—*Progression of Electrocardiographic Pattern of 52 Children with Ventricular Defect*

	Followed for one year or longer* (52)			
	24		28	
Initial ECG	Under age one year		Over age one year	
Later ECGS	Unchanged	Changed	Unchanged	Changed
	18	6	21	7

*Average follow-up 5 years.

also had large left-to-right shunts, had the smallest atrioventricular differences. The right atrial mean pressures with few exceptions were under 10 mm. Hg. The mean "pulmonary capillary wedge" pressures, reflecting left atrial pressure, were over 15 mm. Hg in 9 of 58 patients. Thirty-three of the patients with pulmonary vascular obstruction and 6 of the patients with pulmonary stenosis had a mean pulmonary artery pressure over 40 mm. Hg. The average systolic, diastolic, and pulse pressures of the pulmonary and systemic arteries are presented in table 9. The systemic arterial systolic pressure and the right ventricular systolic pressure were virtually identical (difference less than 20 mm. Hg) in 37 patients, the majority having pulmonary vascular obstruction. Table 9 also presents a survey of the systemic arterial oxygen saturation. It may be seen that there were 24 children with arterial saturation less than 94 per cent, but only 5 below 90 per cent. As mentioned before (table 3) 11 of these children with arterial unsaturation were recognized clinically to be cyanotic; 6 of the unrecognized ones were infants.

Course and Prognosis

Fifty-two patients were followed for 1 year or longer with an average follow-up of 5 years; 49 of these are alive at present. One of the 3 died after cardiac catheterization, the second one with equivocal catheterization findings during exploratory thoracotomy to exclude a patent ductus arteriosus, and a third at another hospital in congestive failure. Of the 48 patients first seen in infancy, 38 have been subsequently examined and all of these with the exception of the one lost at cardiac catheterization are living.

Our pathology department was consulted to determine the number of patients with uncomplicated ventricular septal defect autopsied in this hospital in the six years covered by this report. Five additional patients with ventricular septal defect who were autopsied but not included in the clinical data were found. Patients with ventricular septal defect who had additional cardiac defects, outside the scope of this paper, were excluded. The pertinent autopsy data in the 8 patients representing our total autopsy material on ventricular septal defects are presented in table 10. The size of these defects was related to the aortic valve size as suggested by Selzer.[10]

Two of these infants died within hours after admission to the hospital, not having been recognized as patients with congenital heart disease previously. Probably the patent ductus arteriosus and the aortic valve abnormality contributed to the demise of case 2. Whether functional tricuspid or mitral incompetence was present in case 4 can hardly be accurately determined at autopsy; however, the valves were opaque and obviously abnormal. It is difficult to imagine how the minute ventricular defect in case 5 could have been responsible for the death of the patient.

It is worth noting that all but the 2 children lost during operative procedures had severe pneumonia, a frequent cause of death in infancy by itself.

Progression of Symptoms. The progression of symptoms over the years, as estimated by personal observation and the narrative of the

TABLE 14.—*Detailed Analysis of Electrocardiographic Changes in 13 Children*

Electrocardiographic pattern	Changing electrocardiographic pattern					
	Under age 1 year (6 children)		Over age 1 year (7 children)			
	Normal	Right ventricular hypertrophy	Normal	Right ventricular hypertrophy	Left ventricular hypertrophy	Combined ventricular hypertrophy
Initial electrocardiogram	5	1	1	4	1	1
Last electrocardiogram:						
Right ventricular hypertrophy	1				1	
Left ventricular hypertrophy	3		1	1		1
Combined ventricular hypertrophy	1	1		3		

parent, is recorded in table 11. It can be seen that approximately one half of the patients had mild symptoms in infancy; most of these individuals remained symptomatically stable and only 9 out of the 52 showed definite deterioration. Approximately one third (15 of the 43 patients with severe symptoms in early life) improved. When last seen, roughly 40 per cent continued to have severe symptoms (37), and some of these patients were still in infancy.

Progression of Signs. The obvious difficulty in quantitative appraisal of the physical findings prompted us to analyze only those features that lend themselves most easily to such an analysis. Table 12 presents the changes in weight in 32 children, first seen under age 1 year and followed for at least 2 years. It may be seen that only 1 in this group, a boy with a large left-to-right shunt and marked aortic regurgitation, deteriorated significantly. Nine improved appreciably and the majority stayed in the same developmental channel.

There were 2 patients who lost their marked precordial thrill when congestive failure appeared; on adequate therapy the thrill reappeared. With the exception of these 2 individuals there were no significant changes in the intensity of the systolic murmur. Determination of the presence or absence of a low-frequency diastolic murmur is difficult in infancy; thus the time of discovery may not coincide with its appearance. Contrariwise, it seemed significant to us that in at least 3 children, well-documented apical diastolic murmurs disappeared as they grew older and their general condition improved.

Progression of Electrocardiographic Findings. Fifty-two patients had multiple electrocardiograms taken over a period of 1 or more years. Of these, 24 were under 1 year of age when the first electrocardiogram was taken. Eighteen of these 24 have shown no significant changes despite observations as long as 6 to 7 years in some cases. Of the 28 patients whose first electrocardiogram was taken after the age of 1 year, there were 7 who developed a subsequent change in pattern (table 13).

Table 14 presents a detailed analysis of the changes in the electrocardiograms in 13 children.

Only 2 of the entire group of 13 patients with a changing electrocardiographic pattern developed signs of right ventricular hypertrophy. One, at age 2 years, developed abnormal right ventricular hypertrophy having previously had a normal electrocardiogram, and the second switched from left ventricular hypertrophy at age of 8 years to right ventricular hypertrophy at age 11 years while developing the clinical picture of the tetralogy of Fallot (fig. 10). Six—all with uncomplicated large left-to-right shunts—of the 13 developed pure left ventricular hypertrophy, and 5, all proved to have pulmonary vascular obstruction, developed combined ventricular hypertrophy.

The patients with large uncomplicated left-to-right shunts were the most likely to have shown a changing electrocardiographic pattern; 8 of 13 showed this change. Four patients had pulmonary vascular obstruction and 1 had associated pulmonary stenosis.

Progression of X-ray Findings. There were 42 patients with x-ray examinations extend-

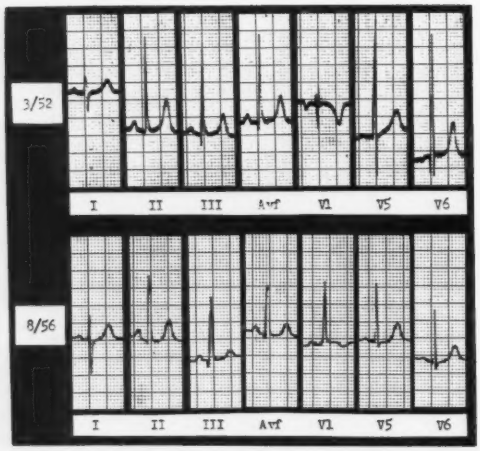


FIG. 10. Change from left ventricular hypertrophy to right ventricular hypertrophy in electrocardiogram in a 3½-year period in an 8-year-old child with ventricular defect and pulmonary stenosis. During the same period the gradient across the pulmonary valve increased from 60 to 100 minutes and arterial unsaturation developed.

ing over a period of more than 1 year. Two of these showed increasing heart size through the years, while in 11 the cardiothoracic ratio decreased. The pulmonary vasculature became progressively increased in 4 patients, while decreasing pulmonary vasculature was found 11 times. Twenty-two patients showed no change at all. Most of the changes occurred when the follow-up examination extended over 5 years and included infancy.

One of the remarkable changes was the decrease in heart size and pulmonary vasculature noted in 2 patients with small uncomplicated left-to-right shunt (fig. 11). A similar change in size and an even more marked diminution of the size of the pulmonary vasculature was noted in some patients with pulmonary stenosis; 1 of these developed the tetralogy of Fallot syndrome (fig. 12). The changes noted in the pulmonary vascular obstruction group and the large uncomplicated left-to-right shunts were not striking.

Catheterization. Eight patients in this series were recatheterized 2 to 7 years after the original study and showed no significant change in any respect. The detailed results of these investigations will be reported in a separate communication.

CONCLUSIONS

General

It is our impression that the 4 hemodynamic variants of ventricular septal defect (uncomplicated large or small left-to-right shunts, associated pulmonary stenosis or pulmonary vascular obstruction) represent a wide spectrum of physiologic situations. Our data suggest that the clinical findings also show a similar pattern.

The size of the shunt may change with the growth of the patient. Although we do not have enough repeated cardiac catheterizations on individual patients to prove this point, the findings relative to the natural history of the disease suggest this possibility. There are individuals in the uncomplicated small left-to-right shunt group who, prior to catheterization, had distinct improvement in heart size, pulmonary vascular engorgement, growth, and symptoms. Contrariwise, there was evidence in some of our patients, particularly in the uncomplicated large left-to-right shunts, of deterioration through the years prior to catheterization as shown by late appearance of severe symptoms, electrocardiographic abnormalities and congestive heart failure. Although these changes in either direction may depend on causes other than variation in the size of the shunt (i.e., myocardial factors), the possibility that this is the underlying reason has to be considered. This changing clinical picture demonstrates the difficulties of rigid classification according to shunt size.

Similar phenomena are observed in children with ventricular septal defect and associated pulmonary stenosis. There are patients with evidence of a large left-to-right shunt and minimal pulmonary stenosis in infancy who develop through the years into "acyanotic" instances of tetralogy of Fallot, showing definite arterial unsaturation on exercise.[11]

Interestingly enough, the group with pulmonary vascular obstruction has been the most stable in our entire series. In contrast to the opinions of others,[12, 13] we have failed

to find significant progression in the clinical picture of any of our patients with pulmonary vascular obstruction. Although we do not doubt that deterioration does occur later in life, we have no evidence that it has happened to any of the children studied by us.

Not only do some of the patients with ventricular septal defect change their clinical profile with time, but also the differences between the individual groups are not sharp ones. Obviously there are children with small shunts, others with very large ones, but there is a middle group that is hard to classify accurately except in a most arbitrary fashion. Similarly, it is difficult to define the difference between an uncomplicated ventricular septal defect and a ventricular defect with associated pulmonary stenosis, since the size of the gradient across the right ventricular outflow tract required to have anatomic stenosis varies with the size of the pulmonary flow. Finally, the arbitrariness of assigning numerical values to the cross-section of the pulmonary vasculature and classifying on that basis is self evident.

Once it has been made clear, however, that the division of patients with ventricular septal defect into subgroups is a difficult task, one should consider the other side of the question and recognize that a working classification is necessary for clinical management, including selection of patients for surgery. Consequently, after defining the clinical data of the entire group, the 4 main physiologic subgroups will be summarized and the individuals with aortic regurgitation will comprise a fifth group.

Profile of Patients with Ventricular Septal Defect

Children with ventricular septal defect and left-to-right shunt all have a moderate to loud systolic murmur at the lower left sternal border and rarely at the apex. This murmur can be heard in the vast majority early in infancy. In a large percentage an accompanying thrill is present. A low-frequency diastolic murmur is noted in about three fourths of the children. Left chest prominence is present in about the same proportion of the cases. On the whole, the growth pattern is usually below average. The symptomatology varies a great deal, but it is more severe (with notable exceptions) in infancy. Cardiac enlargement with pulmonary vascular engorgement characterizes the radiographic picture. The electrocardiogram is usually abnormal; ventricular hypertrophy of one type or another is present in most, and incomplete right bundle-branch block is noted in over 50 per cent of the cases. The prognosis is good, death beyond the neonatal period is rare, and two thirds of the patients are quite stable throughout childhood, some even improving.

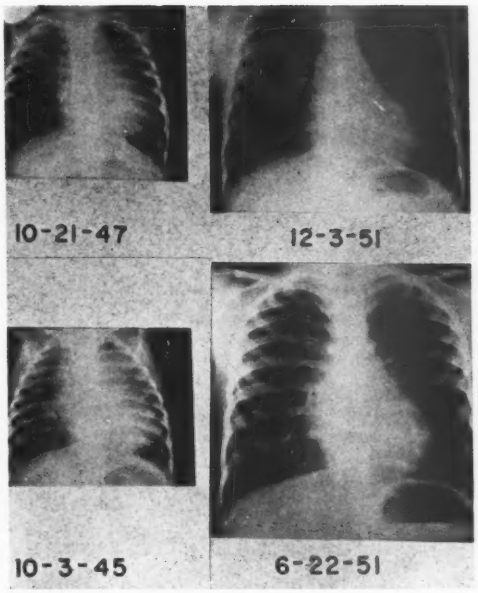


FIG. 11. Radiograms of 2 patients with ventricular defect and small left-to-right shunt. Both the top 2 and the bottom 2 pictures show marked diminution in heart size and pulmonary vasculature.

Small, Uncomplicated Left-to-Right Shunt. This group most nearly approximates the concept of Roger's disease although even these children have symptoms; however, the symptomatology is milder than in some of the other groups and it does not seem progressive. As to the physical findings, it is worth noting that cyanosis is absent and the second heart sound at the pulmonary area is normal or only slightly accentuated. The heart is of

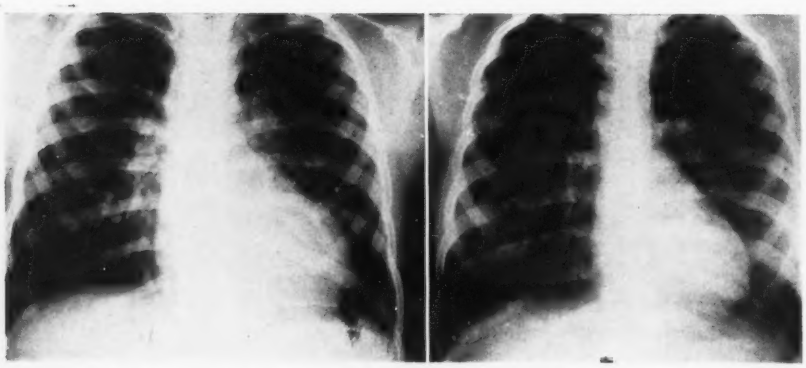


FIG. 12. Two radiograms at 5-year interval of a patient with ventricular defect and pulmonary stenosis. In 1951 the heart is large, the vasculature engorged, and the shunt is exclusively in left-to-right direction. In 1956 the heart is small, the vasculature diminished, and the shunt is right-to-left.

normal size or is only moderately enlarged, the enlargement involving the right or both ventricles. The main pulmonary artery segment and the left atrium tend to be of normal size. "Hilar dance" is unusual. The electrocardiogram shows normal left ventricular dominance or left ventricular hypertrophy. None of the patients in this group showed right axis deviation or pure right ventricular hypertrophy; P-wave abnormality was very uncommon.

Large Uncomplicated Left-to-Right Shunt. These children have more marked symptoms than those with small shunts. Late appearance of symptoms is not uncommon; all of the patients whose congestive heart failure first appeared after age 4 to 5 years belonged to this category. At physical examination a systolic thrill and an apical diastolic rumbling murmur are almost invariably present, while an early diastolic blowing murmur is not uncommon. The second heart sound at the pulmonary area is frequently accentuated. Electrocardiographic evidence of left ventricular hypertrophy is the commonest finding, though combined hypertrophy and normal left dominance is seen. On x-ray the heart tends to be large with pulmonary vascular engorgement, "hilar dance," left atrial enlargement, and considerable enlargement of the main pulmonary artery.

Ventricular Defect with Pulmonary Stenosis. The symptoms are not unlike those seen in the large left-to-right shunt group. At physical examination the loud systolic murmur and thrill is occasionally noted to be maximal at the upper left sternal border. The second heart sound at the pulmonary area is of normal or decreased intensity in the majority. The electrocardiograms show right or left ventricular hypertrophy and only rarely combined hypertrophy. Radiograms usually reveal a distinctly enlarged heart. Expansile pulsations are uncommon, as are left atrial enlargement and enlargement of the main pulmonary artery segment.

Ventricular Defect with Pulmonary Vascular Obstruction (? Eisenmenger Syndrome). The symptoms in these patients vary from mild to quite severe. At physical examination the systolic murmur is commonly of low intensity and occasionally maximal at the apex. A thrill is less frequent than in the other groups. The second heart sound at the pulmonary area is invariably very loud and an early diastolic blowing murmur is common. The electrocardiogram shows pure right ventricular hypertrophy or combined ventricular hypertrophy in almost every case. At x-ray, cardiac enlargement with pulmonary vascular engorgement is the rule, "hilar dance," left atrial enlargement, and an enlarged main pul-

monary artery segment are frequently seen. The patients with smaller hearts at x-ray probably represent dominantly pulmonary vascular obstruction with only a minimal left-to-right shunt. It is understandable that few examples of this would be seen in our group, since a measurable left-to-right shunt was a prerequisite for being included in the series.

Ventricular Septal Defect with Aortic Regurgitation. The 5 patients with aortic regurgitation accounted for 2 of the 3 patients in this series with subacute bacterial endocarditis and 2 of the 5 with episodes of paroxysmal tachycardia. In general, the symptoms were marked and in one instance were distinctly progressive. At physical examination a characteristic loud to-and-fro systolic-diastolic murmur was heard. The systemic pulse pressure was wide. The electrocardiogram showed marked left ventricular hypertrophy with S-T and T-wave changes in the 4 older children. At x-ray, the heart was markedly enlarged with an unusually prominent aorta. The exclusion of a patent ductus arteriosus even by cardiac catheterization is difficult and may require retrograde aortography or exploratory thoracotomy.

Surgical Considerations

Children with a clinical picture of uncomplicated small ventricular septal defect, i.e., individuals with a small heart and a normal electrocardiogram, should have close periodic re-examinations. Catheterization is not imperative, and operation at the present stage of cardiac surgery with the available information on natural history is not indicated.

Children with at least moderate cardiac enlargement and left ventricular hypertrophy by electrocardiogram represent the group to be considered primarily for operation. These are the individuals with a large left-to-right shunt with or without pulmonary stenosis. Cardiac catheterization followed by surgery should be mandatory as soon as a safe operation is available.

Children with cardiac enlargement and combined ventricular hypertrophy should be catheterized to measure the level of pulmonary vascular resistance and the size of the left-to-right shunt. If the resistance is—arbitrarily—below 6 resistance units and the shunt is large, surgery is recommended. In cases with resistance units greater than 12, operation is probably dangerous enough (based on our experience with patent ductus arteriosus and atrial septal defect) to be postponed at least for the time being. The intermediate cases should be judged on their own merits. Children with pure right ventricular hypertrophy, irrespective of heart size, have either associated pulmonary vascular obstruction or pulmonary stenosis. The clinical differentiation between these 2 types should present no real difficulties. Those with pulmonary stenosis are candidates for surgery and those with pulmonary vascular obstruction (with this type of electrocardiogram) probably have too high a resistance to risk operation.

Our experience suggests that not only is the over-all mortality from ventricular septal defect relatively small but also the development or progression of pulmonary vascular disease in small children must be an unusual occurrence. Therefore, there appears to be little point in taking the added risk of surgery in the form of a Dammann operation except in extreme cases.

Summary

1. Ninety-eight patients (average age 6 years) with ventricular septal defect proved at cardiac catheterization were reviewed in detail and summarized in regard to their clinical profile and catheterization data.

2. The various subgroups (uncomplicated small left-to-right shunts, uncomplicated large left-to-right shunts, associated pulmonary stenosis, associated pulmonary vascular disease, associated aortic regurgitation) present a spectrum of physiologic findings each blending into the other; however, each subgroup is clinically recognizable in most instances.

3. The electrocardiogram not only gives considerable information in regard to physiologic diagnosis, but also is useful in selecting patients likely to benefit from surgery. a. In the

absence of pulmonary stenosis (clinically recognizable), pure right ventricular hypertrophy almost excludes the possibility of surgery. b. Pure left ventricular hypertrophy is found almost exclusively in suitable candidates for surgery. c. Patients with combined hypertrophy will require cardiac catheterization to determine whether surgery at a reasonable operative risk will be possible.

4. Follow-up data covering 1 to 13 years (average 5 years) on approximately 50 per cent of cases was presented.

5. No clinical evidence for the development or increase of pulmonary vascular disease was noted in this group of children.

6. Late clinical deterioration was noted mainly in those children with large left-to-right shunts without pulmonary vascular obstruction or pulmonary stenosis.

7. A single patient with associated pulmonary stenosis progressed from a large left-to-right shunt to the tetralogy of Fallot syndrome.

8. The prognosis of children with ventricular septal defect appears to be good after infancy for a matter of several years; only 1 child died because of his ventricular defect in this series of 98 catheterized patients.

9. The autopsy data on 5 additional small infants with ventricular defect who died during the period covered by this study are presented.

Summario in Interlingua

1. Un serie de 98 patientes (etate medie: 6 annos) con defectos ventriculo-septal a demonstration per catheterisation cardiac esseva studiate detaliatemente con respecto a lor profilos clinic e al datos de catheterisation.

2. Le varie sub-gruppos—non-complicate miere derivationes sinistro-dextere, non-complicate grande derivationes sinistro-dextere, associate stenosis pulmonar, associate morbo pulmono-vascular, associate regurgitation aortic—presenta un spectro de constatationes physiologic con transitiones gradual inter le sub-gruppos. Nonobstante, in le majoritate del casos, le sub-gruppo in question es clinicamente recognoscibile.

3. Le electrocardiogramma provide non solmente inportante informationes pro le diagnose physiologic; illo es etiam utile in seliger patientes qui pote beneficiar ab le therapia chirurgic. (a) In le absentia de stenosis pulmonar (clinicamente recognoscibile), hypertrophia dextero-ventricular pur exclude virtualmente le possibilitate de un intervention chirurgic. (b) Hypertrophia sinistro-ventricular pur occurre quasi exclusivemente in individuos que es bon canditatos pro un intervention chirurgic. (c) Patientes con hypertrophia combinate require catheterisation combinate pro determinar si un intervention chirurgic es possibile sin excessive riscos operatori.

4. Datos de observationes consecutori, colligite durante inter 1 e 13 annos (periodo medie: 5 annos) es presentate pro approximativemente 50 pro cento del casos.

5. Nulle signos clinic del disveloppamento o augmento de morbo pulmono-vascular esseva notate in iste gruppo de pueros e pueras.

6. Tardive deterioration clinic esseva notate principalmente in individuos con grande derivationes sinistro-dextere sin obstruction pulmono-vascular o stenosis pulmonar.

7. Un sol patiente con associate stenosis pulmonar progredeva ab un grande derivation sinistro-dextere al syndrome del tetralogia de Fallot.

8. Le prognose pro juveniles con defecto ventriculo-septal es apparentemente bon pro plure annos post le infantia. Solmente 1 patiente moriva a causa de su defecto ventricular in iste serie de 98 pueros e pueras catheterisate.

9. Es presentate in plus le datos necroptic ab 5 juvenissime infantes con defecto ventricular qui moriva durante le periodo coperite per le presente studio.

REFERENCES

1. Kirklin, J. W., Donald, D. E., Harshbarger, H. G., Hetzel, P. S., Patrick, R. T., Swan, J. C., and Wood, E. H.: Applicability of the Gibbon type oxygenator to human intracardiac surgery. Ann. Surg. **144:** 2, 1956.
2. DeWall, R. A., Warden, H. E., Read, R. C., Gott, U. L., Ziegler, N., Varco, R. L.,

AND LILLIHEI, C. W.: A simple, expendable, artificial oxygenator for open heart surgery. Surg. Clin. North America **36**: 1025, 1956.
3. COOLEY, D. A., BELMONTE, B. A., DEBAKEY, M. E., AND LATSON, J. R.: Temporary extracorporeal circulation in the surgical treatment of cardiac and aortic disease. Ann. Surg. **145**: 898, 1957.
4. DAMMANN, J. F., JR., AND MULLER, W. H., JR.: The role of the pulmonary vascular bed in congenital heart disease. Pediatrics **12**: 307, 1953.
5. GORDY, E., AND DRABKIN, D. L.: Simplified spectrophotometric technique applicable to standard equipment for the determination of O_2 saturation of blood. Am. J. M. Sc. **221**: 231, 1951.
6. FRIEDLICH, A., BING, R. J., AND BLOUNT, S. G., JR.: Circulatory dynamics in the anomalies of venous return to the heart including pulmonary arteriovenous fistula. Bull. Johns Hopkins Hosp. **86**: 20, 1950.
7. KJELLBERG, S. R., MANNHEIMER, E., RUDHE, U., AND JONSSON, B.: Diagnosis of Congenital Heart Disease. Chicago, The Year Book Publishers, Inc., 1955.
8. NADAS, A. S.: Pediatric Cardiology. Philadelphia, W. B. Saunders Company, 1957.
9. WOOD, P., MAGIDSON, O., AND WILSON, P. A. O.: Ventricular septal defect with a note on acyanotic Fallot's tetralogy. Brit. Heart J. **16**: 387, 1954.
10. SELZER, A.: Defect of the ventricular septum. Arch. Int. Med. **84**: 798, 1949.
11. RUDOLPH, A. M., NADAS, A. S., AND GOODALE, W. T.: Intracardiac left to right shunt with pulmonic stenosis. Am. Heart J. **48**: 808, 1954.
12. BLOUNT, S. G., JR., MUELLER, H., MCCORD, M. C.: Ventricular septal defect. Am. J. Med. **18**: 871, 1955.
13. ADAMS, F. H.: Pulmonary hypertension in children due to congenital heart disease. J. Pediat. **40**: 42, 1952.

Schlachman, M.: The Failure of Anticoagulant Therapy to Prevent Myocardial Infarction in Patients with Premonitory Symptoms of an Impending Coronary Occlusion. Ann. Int. Med. **46**: 728 (Apr.), 1957.

Reports have appeared in the literature which indicate that the long-term use of anticoagulants is effective in preventing recurrent coronary occlusion. On the basis of these results, it has been implied that anticoagulants can be used in patients with impending coronary occlusion with the hope of preventing a frank coronary thrombosis. In this communication, there are described the details in connection with the illness and treatment of 3 patients all of whom had definite premonitory symptoms of an impending coronary thrombosis. The 3 patients were hospitalized immediately after the onset of their symptoms and anticoagulant therapy was initiated in the form of intramuscular injections of 150 mg. of a concentrated aqueous solution of sodium heparin administered at intervals of 8 hours. Under the conditions of this method of administration of anticoagulant therapy, which was considered as completely adequate, all 3 patients developed acute coronary occlusion with typical electrocardiographic changes. One of the patients experienced occlusion after a week of continuous anticoagulant therapy; the other 2 developed the coronary occlusion 48 hours after the start of treatment with anticoagulant. Since hemorrhage, either as a result of rupture of an atheromatous plaque or as a result of intimal changes secondary to intramural hemorrhage because of rupture of vasa vasorum, can precede a coronary occlusion, it is not to be expected on theoretic grounds that anticoagulant therapy can modify or prevent the rupture of these subintimal capillaries and thereby prevent coronary thrombosis with coronary occlusion. This could be an explanation for the failure of anticoagulant therapy to prevent myocardial infarction in the 3 patients described in this report.

WENDKOS

Reverse Wenckebach Block and Complete Atrioventricular Dissociation due to Potassium and Digitalis

By CHARLES FISCH, M.D., AND ANTHONY S. RIDOLFO, M.D.

The relation of digitalis to potassium was studied by administering potassium intravenously before and after digitalization. The disturbances of conduction due to potassium and those occurring after digitalis were observed and are here discussed.

POTASSIUM is an effective agent for the control of arrhythmias associated with digitalis and hypopotassemia and of many arrhythmias of obscure etiology.[1-5] The therapeutic effect of potassium in cardiac irregularities caused by digitalis has been ascribed to a digitalis and potassium "antagonism." For a demonstration of this antagonism, potassium was administered intravenously to patients with atrial fibrillation after they were "fully" digitalized. The end point of digitalization was shown by a marked depression of atrioventricular (A-V) conduction and the appearance of A-V nodal escape beats, A-V nodal rhythm, ventricular bigeminy with varying configuration of the ectopic beats and, finally, failure to speed significantly the ventricular rate by intravenous administration of 1.25 to 2.0 mg. of atropine. It was assumed that in such patients, after treatment with potassium, the digitalis-potassium antagonism would be manifested by an increase of conduction via A-V node with disappearance of A-V nodal arrhythmias and speeding of ventricular rate. Surprisingly, however, in the majority of patients the conduction in the A-V node was depressed further with the appearance of complete A-V dissociation, ventricular escape beats, and idioventricular rhythm. In short, the electrocardiogram looked as if the digitalis had exerted a greater effect and not been antagonized by the potassium.[6]

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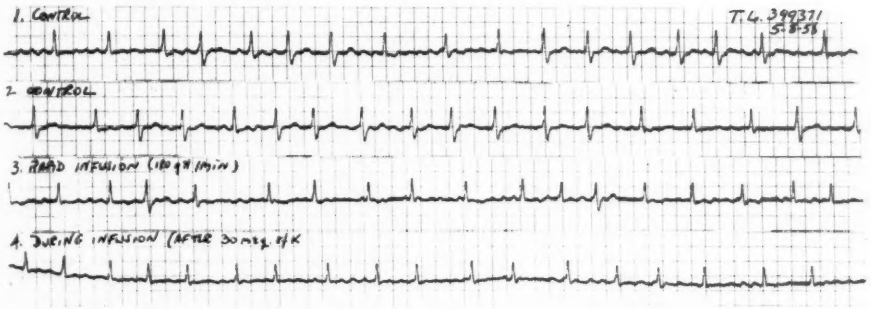
Supported by The Herman C. Krannert Fund of The Indiana Heart Foundation and Indiana State Board of Health.

The case reported in this paper is one of a large number of cases of atrial fibrillation, treated with potassium over the past 2 years. It is considered that this particular case is worthy of detailed description as it demonstrates (1) reverse Wenckebach periods, an extremely rare phenomenon, (2) the ability of potassium to cause complete A-V dissociation, a finding not previously observed in human beings in the presence of sinus rhythm,[7, 8] (3) the obvious "additive effect" of potassium and digitalis, and (4) hazards of rapid administration of potassium to an overdigitalized patient, as contrasted with one who is not digitalized.

CASE REPORT

An 82-year-old man was admitted to Indianapolis General Hospital for the control of atrial fibrillation caused by coronary heart disease. The patient had not been previously treated for heart disease and had never received digitalis. Significant physical findings were atrial fibrillation and moderate cardiac enlargement. No clinical signs of heart failure were noted. Laboratory procedures, including complete blood count, urinalysis and blood urea nitrogen, were normal. Plasma serum potassium was 4.5 mEq./L. An electrocardiogram showed atrial fibrillation.

On May 8, 1958, 40 mEq. of an isotonic solution of potassium phosphate in distilled water was administered intravenously over a period of 50 minutes. The rate of infusion varied from 30 drops to 180 drops per minute, depending on the severity of pain at the site of injection. Figure 1 shows the effect of potassium. *Strips 1* and *2* (control tracing) disclose atrial fibrillation with a ventricular rate of 90 beats per minute and aberrant ventricular conduction. Within 3 minutes of onset of rapid infusion (180 drops per minute) the aberrant conduction became less frequent (*strip 3*), finally disappeared and did not reappear during the period of observation. The conduction through the A-V node and the ventricular rate remained unchanged (*strip 4*



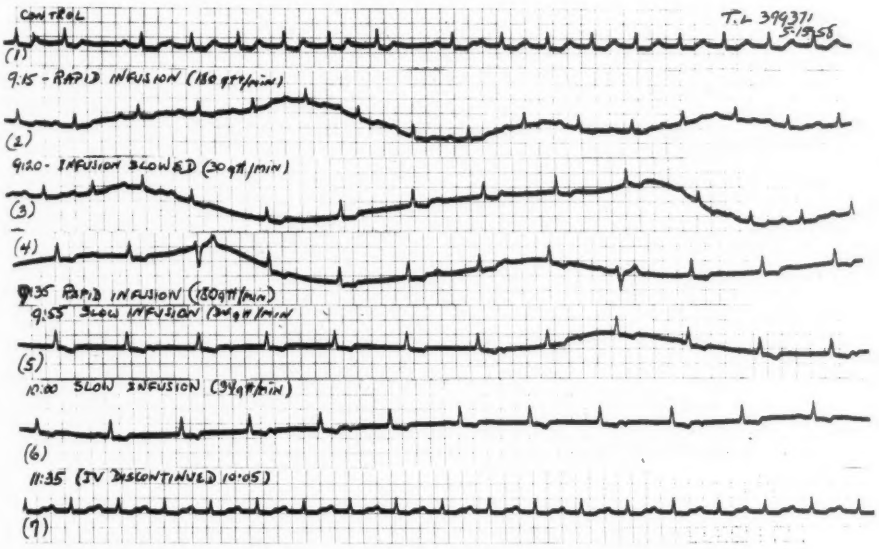


FIG. 1 *Top.* Electrocardiogram May 8, 1958.

FIG. 2 *Bottom.* Electrocardiogram May 15, 1958.

In the next week the patient was given 2.0 mg. of digitoxin. On May 15, 1958, the day the infusion of potassium was to be repeated, the patient exhibited sinus rhythm with delayed A-V conduction (fig. 2). The P-R interval measured 0.24 to 0.30 second. Two Wenckebach periods were noticed (*strip 1*). Because it was thought that the electrocardiographic and clinical findings were those of digitalis toxicity, potassium was administered in the manner described. *Strip 2* illustrates changes during rapid infusion of potassium with resultant slowing of the ventricular rate from 100 to 60 beats per minute without any change of the P-R interval. This effect was probably mediated through the vagus nerve. Shortly after the infusion was slowed, the P waves became lower in amplitude, and periods of complete A-V dissociation occurred with an A-V nodal rate of 60 beats per minute and a retrograde P wave after the ninth ventricular complex (*strip 3*). These changes persisted for a few minutes, after which sinus rhythm with first-degree block returned. At that time the solution was changed to isotonic potassium phosphate in 5 per cent glucose, to diminish the pain at site of injection; for a short period of time rapid infusion was reinstituted (*strip 4*). The A-V dissociation with A-V nodal rhythm promptly reappeared, P waves became smaller, and 2 ventricular escape beats were observed (*beats 3* and *9*). At this point the infusion was slowed from 180 drops per minute to 30 drops per minute and this rate was maintained until the entire 40 mEq. were given. *Strip 5* shows the persistence of complete forward block but with preservation of retrograde conduction, as shown by the appearance of retrograde P waves after

complexes 2 and 9 with an R-P of 0.40 to 0.48 second measured from beginning of R to nadir to P. The R-P interval following the last beat in this strip is 0.40 second. *Strip 6* shows complete unidirectional block. Retrograde P waves are present after ventricular beats 3, 4, and 5 with a R-P of 0.24, 0.40 and 0.48 second respectively, and again after beats 9 and 10 with a R-P of 0.40 and 0.46 second. It is uncertain whether or not a retrograde P wave is buried in the S-T segment of ventricular complex 8. Shortly after the infusion was discontinued sinus rhythm returned, first alternating with second-degree block and stabilizing 30 minutes after the infusion was discontinued as a first-degree block with occasional Wenckebach periods (a situation identical to that present before infusion of potassium). This rhythm remained unchanged during the period of observation (*strip 7*).

Comment

There is no doubt that this tracing demonstrates periods of unidirectional (forward) heart block as well as periods of complete block. In the former the retrograde conduction from the A-V node to the atria has the classical Wenckebach structure. In strip 6, 3 consecutive retrograde P waves are visible; the largest increment in time of conduction toward atria is between the first and second complex (0.16 second), and this increase is less between the second and third P wave (0.08 second). The disturbance of A-V conduction was probably as much a result of the vagal as of the direct depressing effect of potassium on the conduction tissue.

It was thought that the failure to depress the A-V conduction, and thus to slow the ventricular rate before the patient was digitalized, was of some clinical significance. The disappearance of aberrant conduction during the initial infusion without slowing of the ventricular rate suggests improvement rather than depression of impulse conduction. The failure to slow appreciably the ventricular rate in undigitalized or poorly digitalized patients with atrial fibrillation has been confirmed many times during our study.[9] One cannot escape the thought that in this case the digitalis has in some way potentiated the toxic effects of potassium. That the reverse is less likely is attested to by the transient nature of the changes observed. The substitution of isotonic potassium phosphate in 5 per cent glucose for the same in distilled water does not confuse the immediate results. The slowing of sinus rhythm, complete A-V dissociation and retrograde conduction appeared before the solution was changed (*strips 1-3*). It is impossible to state with certainty whether or not the glucose, by combining with potassium subsequently affected the serum or intracellular myocardial potassium, and thus contributed to the toxic effects observed.

It seems reasonable to assume that digitalis toxicity, which becomes manifest as a result of potassium depletion,[10] may represent an entirely different problem from toxicity due primarily to administration of large doses of digitalis. In the former potassium is beneficial; in the latter, however, it may aggravate the situation by its well-known nonspecific depressing effect on the heart. Further study of this problem is essential.

Summary

A case is presented in which (1) the toxic effects of potassium on the myocardium became manifest only after digitalization, (2) the effect of potassium was one of depression of atrioventricular conduction to the point of complete atrioventricular dissociation, with periods of retrograde conduction manifesting the classical Wenckebach structure.

The "additive" effects of potassium and digitalis are stressed.

Acknowledgment

We wish to thank Dr. Kenneth G. Kohlstaedt, Chief, Cardio-Vascular Division, for his continuous support and encouragement.

Summario in Interlingua

Es presentate un caso in que (1) le effectos toxic de kalium super le myocardio deveniva manifeste solmente post digitalisation e in que (2) le effecto le kalium consisteva in le depression del conduction atrioventricular usque a su dissociation complete, con periodos de conduction retrograde exhibiente le classic structura de Wenckebach.

Le effectos "additive" de kalium e digitalis es aublineate.

REFERENCES

1. AMPSON, J. J., AND ANDERSON, E. M.: The therapeutic use of potassium in certain arrhythmias. Proc. Soc. Exper. Biol. & Med. **28**: 163, 1930.
2. —, AND —: Treatment of certain cardiac arrhythmias with potassium salts. J.A.M.A. **99**: 2257, 1932.
3. ENSELBERG, C. D., SIMMONS, H. G., AND MINTZ, A. A.: The effects of potassium upon the heart with special reference to the possibility of treatment of toxic arrhythmias due to digitalis. Am. Heart J. **39**: 713, 1950.
4. LOWN, B., AND LEVINE, S. A.: Current concepts in digitalis therapy. New England J. Med. **250**: 771, 819, 866, 1954.
5. BETTINGER, J. C., SURAWICZ, B., BRYFOGLE, J. W., ANDERSON, B. N., JR., AND BELLET, S.: The effect of intravenous administration of potassium chloride on ectopic rhythms, ectopic beats and disturbances in A-V conduction. Am. J. Med. **21**: 521, 1956.
6. FISCH, C., SHIELDS, J. P., RIDOLFO, A. S., AND FEIGENBAUM, H.: Effect of potassium on conduction and ectopic rhythms in atrial fibrillation treated with digitalis. Circulation **18**: 98, 1958.
7. LEVINE, H. D., MERRILL, J. P., AND SOMMERVILLE, W.: Advanced disturbances of the cardiac mechanism in potassium intoxication in man. Circulation **3**: 889, 1951.
8. ENSELBERG, C. O., SIMMONS, H. G., AND MINTZ, A. A.: The effect of potassium upon the heart with special reference to the possibility of treatment of toxic arrhythmias due to digitalis. Am. Heart J. **39**: 713 1950.
9. FISCH, C., AND RIDOLFO, A. S.: The effect of potassium on conduction in nondigitalized or "atropinized" patients with atrial fibrillation. To be published.
10. WELLER, J. M., LOWN, B., HOIGNE, R. V., WYATT, N. F., CRISCITIELLO, M., MERRILL, J. P., AND LEVINE, S. A.: Effects of acute removal of potassium from dogs. Circulation **11**: 44, 1955.

Sanders, R. J., Neubuerger, K. T., and Ravin, A.: Rupture of Papillary Muscles: Occurrence of Rupture of the Posterior Muscle in Posterior Myocardial Infarction. Dis. Chest **31**: 316 (March), 1957.

Rupture of a papillary muscle of the heart has been considered an unusual complication of myocardial infarction. Although first recognized as early as 1803, only 56 cases have been reported to date. Five additional cases are presented in this paper. Rupture of the posterior papillary muscle of the left ventricle is 6 to 12 times more common than rupture of the anterior one, and the former is usually associated with posterior myocardial infarction. Diagnosis of rupture of the papillary muscle should be considered in the presence of acute myocardial infarction, when there suddenly develops a loud apical systolic murmur with sudden onset of shock, dyspnea, and pulmonary edema. The prognosis is extremely poor. Differential diagnosis includes acute cardiac dilatation with mitral insufficiency and perforation of the interventricular septum. Anterior myocardial infarction is found in 75 per cent of the cases of septal perforation, while posterior infarction is just as common among cases of papillary muscle rupture.

MAXWELL

The Diagnosis of Circulatory Shunts by the Nitrous Oxide Test

Improvements in Technic and Methods for Quantification of the Shunt

By Richard J. Sanders, M.D., and Andrew G. Morrow, M.D.

The nitrous oxide test for the detection and localization of left-to-right shunts has previously been studied clinically. Further experience with the method has shown that a higher N_2O concentration and an earlier sampling period result in a larger arteriovenous N_2O difference that increases the sensitivity of the test and further minimizes the importance of possible analytic errors. In addition, a method is described of determining the magnitude of the shunt from the results of a N_2O test. The results of 150 N_2O tests performed with the improved technic are presented, and compared to the results obtained with the O_2 method in a group of patients on whom both tests were carried out.

THE usefulness of the nitrous oxide test in the detection and localization of left-to-right circulatory shunts has been established.[1, 2] The test takes advantage of the large arteriovenous difference following inhalation of an inert gas. In the technic originally described, 15 per cent N_2O was inhaled for 60 seconds as integrated blood samples were drawn simultaneously from the pulmonary artery or a right heart chamber and a systemic artery. The presence or absence of a left-to-right shunt was indicated by the ratio of the N_2O content of right heart or pulmonary arterial blood to that of systemic arterial blood. The superiority of this test over the method of determining O_2 differences was shown in 148 patients in whom both technics were employed.

The experience with 15 per cent N_2O and the 60-second sampling period indicated that in some patients an adequate arterial level was not achieved while in others, particularly in children, a rapidly rising venous level had decreased the arteriovenous difference by the end of this period of time (figs. 1 and 2). Accordingly, studies were undertaken to evaluate different N_2O concentrations and various sampling periods; these have led to an improved method of performing the N_2O test. In addition to the detection and localization of left-to-right shunts, the results of the N_2O test can be used to estimate their magnitudes. This method for quantification as well as the modifications of the original N_2O test are described in the present report.

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Materials and Methods

In 98 patients, 150 satisfactory N_2O tests were performed. With 4 exceptions, all patients had pulmonary artery N_2O tests; in addition, 30 patients had right ventricular tests and 26 had right atrial tests. Sixty-nine of the tests were performed on children under 15 years of age and the remaining 81 on adults.

Seventy-eight tests were performed on 63 patients without left-to-right shunts. Forty-five of these control patients had rheumatic heart disease; the others had various forms of congenital heart disease without a shunt or were children with normal hearts and functional murmurs. Seventy-two tests were carried out in 35 patients with left-to-right shunts. Of these, 16 had atrial septal defects, 15 ventricular septal defects and 2 had patent ductus arteriosus. Of the 2 remaining patients one had an aorticopulmonary window and the other a fistula between the right coronary artery and the right atrium. All patients had confirmatory evidence of the presence or absence of a shunt: in the majority of patients the diagnosis was confirmed at operation, and in the others by other studies including aortic catheterization, right and left heart catheterization,[3] indicator-dilution curves,[4-6] thoracic aortography, and selective angiocardiography.[7, 8]

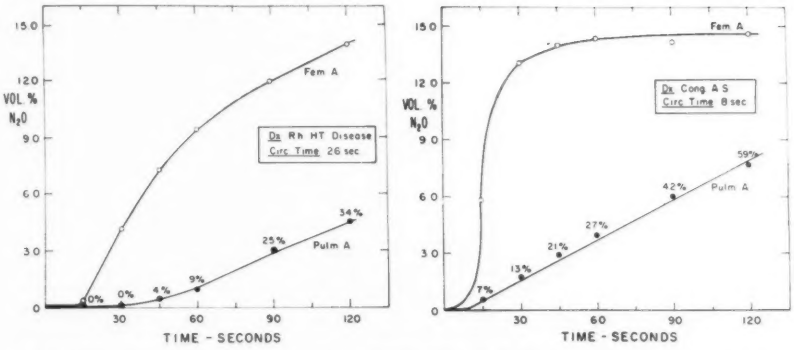

FIG. 1 *Left.* Changes in the arterial and mixed venous blood N_2O content of an adult with rheumatic heart disease and a prolonged circulation time during 2 minutes of 50 per cent N_2O inhalation. The percentages refer to the N_2O content of pulmonary arterial blood expressed as a percentage of the systemic arterial content at that time. There is a long delay before the venous content rises, and it is only 9 per cent of the arterial content at the end of the first minute.

FIG. 2 *Right.* Mixed venous and arterial N_2O contents in a child with a rapid circulation time. The arterial saturation is near completion by 30 seconds, much sooner than in the adult patient in figure 1. The venous level also rises much more quickly, reaching 13 per cent of the arterial level in 30 seconds, and 27 per cent by the end of 1 minute.

The N_2O tests were carried out in the following manner. The tip of a cardiac catheter was placed in a right heart chamber or the main pulmonary artery, and a needle was inserted into a systemic artery. The patient was then instructed to breathe deeply a mixture of 50 per cent N_2O, 20 per cent O_2 and 30 per cent N_2 for 30 seconds.* Integrated blood samples were drawn simultaneously from the catheter and needle during the last 20 seconds of inhalation at the rate of 1 ml. every 4 seconds. The gas was administered through a 3-way valve and either a face mask or mouthpiece. The blood samples were capped and analyzed manometrically for N_2O content.[9]

At least 5 and preferably 10 minutes were allowed for N_2O desaturation before a test was repeated in another heart chamber. A blood specimen for a blank determination was always obtained from the catheter immediately prior to each test. This blank was then subtracted from the N_2O content of each sample and the result of the test was expressed as the ratio of the pulmonary arterial or right heart sample to the arterial sample:

$$\frac{PA.\ RV \text{ or } RA\ N_2O\ content}{Arterial\ N_2O\ content} \times 100$$

From 43 patients (31 with shunts) blood samples were obtained for the determination of O_2 content. Two samples from the pulmonary artery and each vena cava, and 3 samples from each right heart chamber were analyzed. The average O_2 content of blood from each chamber was used to determine the O_2 differences between chambers and to calculate the pulmonary and systemic flows by the Fick method. The samples were analyzed manometrically,[10] with 6 exceptions, in which a spectrophotometric method was employed.[11]

RESULTS

The results of the 150 N_2O tests performed in all 98 patients are presented graphically in figure 3. Between the tenth and thirtieth seconds of inhalation of 50 per cent N_2O, the integrated arterial samples contained 2.0 to 14.0 vol. per cent N_2O. During the period of the study only 5 patients had arterial concentrations of less than 1.5 vol. per cent and these have been excluded, since analytic errors become of increased significance with such low gas concentration. The average arterial N_2O content among the patients with rheumatic heart disease was 6.0 ± 2.8 vol. per cent (median = 5.8 vol. per cent). Adults with congenital heart disease had an average arterial level of 7.5 ± 2.6 vol. per cent (median = 7.4 vol. per cent), and the children had an average level of 7.9 ± 2.5 vol. per cent (me-

*This gas mixture was obtained from the Ohio Chemical Company, Murray Hill, New Jersey.

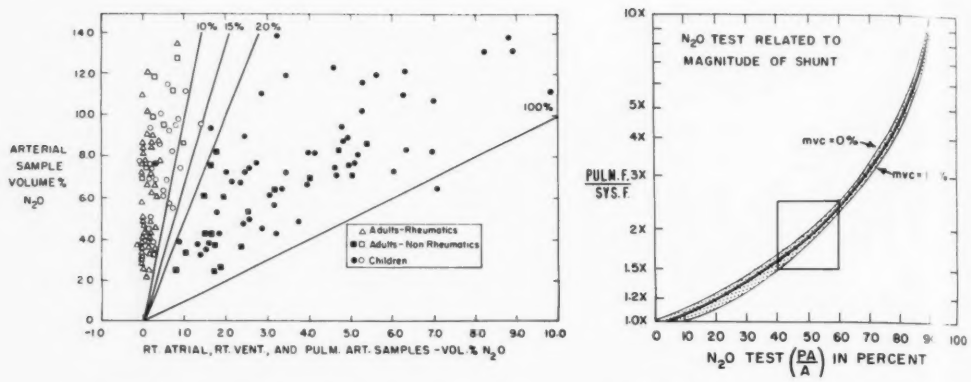

FIG. 3 *Left.* Results of 150 N_2O tests. Open figures represent control patients; solid figures, patients with left-to-right shunts. Percentage lines refer to the ratio of $\frac{\text{RA, RV, and PA samples}}{\text{Arterial samples}} \times 100$. The 15 per cent line appears to separate the shunt and control groups. Among the control patients, those with rheumatic heart disease have lower arterial levels and lower ratios than the nonrheumatic patients.

FIG. 4 *Right.* Conversion of N_2O test into terms relating the pulmonary flow to the systemic flow by comparing the systemic arteriovenous difference in N_2O concentration to the pulmonary arteriovenous difference, or $\frac{100\%-6\%}{100\%-PA\%}$. The solid line represents the related values when the mixed vena caval content is 6 per cent of the arterial content. The shaded area indicates the variations introduced by vena caval levels of 0 to 10 per cent. The box encloses the zone of N_2O tests between 40 and 60 per cent, which relate to pulmonary flows of 1.5 to 2.5 times systemic flows.

dian = 7.6 vol. per cent). In comparison, when 15 per cent N_2O was inhaled and a 1-minute integrated sample was drawn[1] the range of arterial samples was 1.5 to 4.5 vol. per cent and the average was 3.0 vol. per cent. In the present study, with 50 per cent N_2O the arterial level was below 4.5 vol. per cent in only 32 of 137 tests in acyanotic patients; the majority of these patients were among the group with rheumatic heart disease. Patients with right-to-left shunts had lower arterial levels than the noncyanotic group; the average arterial level in 13 cyanotic patients was 3.6 vol. per cent and it exceeded 2.0 vol. per cent in all but 1 instance.

In the absence of a left-to-right shunt the venous N_2O level, measured in either the right atrium, right ventricle or pulmonary artery, was less than 15 per cent of the arterial level, and in all but 5 of the 96 control tests was less than 10 per cent. Again, a difference was found between rheumatic and nonrheumatic control patients. In those with rheumatic heart disease the average venous sample was 2.2 ± 2.4 per cent of the arterial sample. Among the control patients with nonrheumatic types of heart disease the venous samples of adults averaged 4.6 (± 3.4 per cent) while that of children averaged 6.1 (± 4.0 per cent) of the arterial sample. Among all children control tests in the right atrium averaged 6.0 per cent, in comparison to an average value of 6.3 per cent for tests in the right ventricle and pulmonary artery. The 5 control patients whose tests revealed values between 10 and 15 per cent all had congenital heart disease.

Seventy-two N_2O tests were performed in 35 patients with left-to-right shunts. With 1 exception, tests at or beyond the entrance of the shunt revealed venous levels exceeding 15 per cent of the corresponding arterial levels. The single false negative result (4 per cent) was a right ventricular test in a child

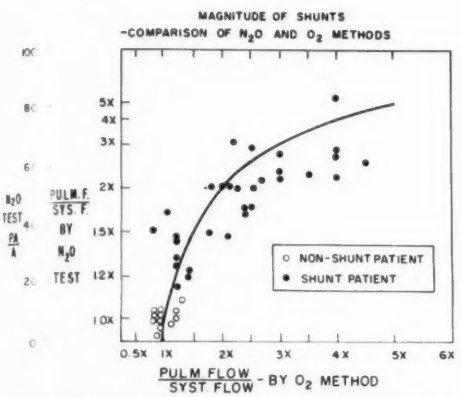

FIG. 5. Magnitude of 31 shunts determined by both the N_2O test and O_2 method. The solid line indicates the points where the determinations by both technics coincide. The second ordinate relates the N_2O test in per cent to the ratio of pulmonary: systemic flow as shown in figure 4.

with a high ventricular septal defect and a small shunt. It is probable that the catheter tip was not high enough in the right ventricular outflow tract for sampling shunted blood, since the pulmonary artery test was higher (17 per cent). The shunt was not revealed by oximetry, and the diagnosis of ventricular septal defect was established by a positive indicator-dilution curve from the left ventricle and a normal curve from the ascending aorta. A thoracic aortogram was also normal. In 1 patient with an atrial septal defect, the right atrial sample was 109 per cent of the arterial sample. Presumably, the catheter tip was lying in or facing the left atrium during the test. A subsequent test in the right ventricle was 51 per cent.

Quantification of the Shunt

The presence of a left-to-right shunt permits the mixing of venous and arterialized blood containing different concentrations of N_2O. The N_2O content of mixed venous blood proximal to the shunt may be assumed to equal that observed in nonrheumatic control patients. This value was found to be 6 ± 6 per cent of the arterial level. The N_2O content of shunted blood may be considered to be essentially the same as that of arterial blood. The N_2O concentration in blood distal to the shunt (usually sampled from the pulmonary artery) reflects the mixing of systemic and shunted flows. Since the pulmonary arterial concentration is measured and the other 2 levels may be closely estimated, the relative amounts of systemic and shunted blood required to produce the observed concentration of N_2O in pulmonary arterial blood can be determined.

Since, in the presence of a left-to-right shunt, the pulmonary flow is equal to the systemic flow plus shunt flow, then the amount of N_2O passing through the pulmonary circuit must be equal to the sum of the amounts returned to the heart from the systemic veins and that added by the shunt:

$$\dot{Q}pa = \dot{Q}sys + \dot{Q}sh \qquad (1)$$

Since the quantity of N_2O traversing any chamber in a given time is equal the product of the blood flow and its N_2O concentration, then:

Pulmonary flow ($\dot{Q}pa$) × *PA* N_2O *test* (Cpa_{N_2O}) = *systemic flow* ($\dot{Q}sys$) × *mixed venous* N_2O *test* (Cvc_{N_2O}) + *shunt flow* ($\dot{Q}sh$) × *arterial* N_2O *level* (Ca_{N_2O})

or

$$\dot{Q}pa\ Cpa_{N_2O} = \dot{Q}sys\ Cvc_{N_2O} + \dot{Q}sh\ Ca_{N_2O} \qquad (2)$$

since

$$\dot{Q}sh = \dot{Q}pa - \dot{Q}sys \qquad \text{(from equation 1)}$$

Substituting equation 1 into equation 2:

$$\dot{Q}pa\ Cpa_{N_2O} = \dot{Q}sys\ Cvc_{N_2O} + (\dot{Q}pa - \dot{Q}sys)\ Ca_{N_2O} \qquad (3)$$

and rearranging:

$$\dot{Q}sys\ (Ca_{N_2O} - Cvc_{N_2O}) = \dot{Q}pa\ (Ca_{N_2O} - Cpa_{N_2O})$$

or

$$\frac{\dot{Q}pa}{\dot{Q}sys} = \frac{Ca_{N_2O} - Cvc_{N_2O}}{Ca_{N_2O} - Cpa_{N_2O}} \qquad (4)$$

The above analysis has been carried out under the assumption that the rate of change of concentrations of N_2O in the blood of the heart chambers is zero. This represents the so-called "steady state" solution of the differential equations governing the system. Some preliminary mathematical analysis has shown that formula 4 is also valid, under conditions thus far investigated, for the more general case where the concentrations of N_2O vary with time.[12]

The formula derived above is similar to that described by others[13, 14] for the application of

the Fick principle in calculating pulmonary and systemic flows with O_2 samples:

$$\frac{Pulmonary\ flow}{Systemic\ flow} = \frac{Ca_{O_2} - Crc_{O_2}}{Ca_{O_2} - Cpa_{O_2}}$$

Both methods of determination are based upon the arteriovenous differences proximal and distal to the shunt. They differ only in that one method utilizes relative blood N_2O concentration and the other blood O_2 content.

When the N_2O arteriovenous difference is used, only the concentration distal to the shunt need be measured, since the concentration proximal to the shunt will be close to 6 per cent of the arterial concentration (fig. 3). Thus, by assuming a normal venous level 6 per cent of the arterial one, it is possible to convert all of the N_2O percentages into ratios relating pulmonary flow to systemic flow (fig. 4). This figure also demonstrates that if the N_2O ratio in blood proximal to the shunt varies from 0 to 10 per cent, the resulting calculation of the magnitude of the shunt is altered only slightly. The enclosed area illustrates that N_2O ratios of 40 and 60 per cent correspond to pulmonary flow: systemic flow ratios of 1.5:1 and 2.5:1 respectively.

When the results of the N_2O tests are expressed as ratios of pulmonary to systemic flow, a basis is provided for comparison with the method of O_2 differences. In figure 5 these ratios calculated by both methods, are plotted for 31 patients with shunts and 12 patients without shunts. With the O_2 method the 7 patients with small left-to-right shunts (plotted on the abscissa in fig. 5) had pulmonary/systemic flow ratios in the range observed among control patients (0.8:1 and 1.3:1). Six of these 7 patients had O_2 step-ups of less than 1 vol. per cent and were thus considered false negative tests by O_2 differences. In comparison, the N_2O calculations in the control patients never indicated pulmonary flows exceeding 1.1 times systemic flow. The 7 patients with shunts who could not be separated from the control patients by O_2 determinations were easily distinguished from the controls by N_2O measurements (see ordinate, fig. 5) although with but one exception the ratio of pulmonary flow to systemic flow was less than 1.5:1.

With larger shunts, the ratios of pulmonary to systemic flow determined by the N_2O method were not so great as those calculated by the O_2 method. In 6 patients the calculated pulmonary flows exceeded 3 times the systemic flows by O_2 determinations; in only 1 of these patients did the ratio exceed this value when calculated by the N_2O method.

The reliability of a single N_2O test for estimating the size of a shunt is demonstrated in figure 6. Twenty-one patients with either atrial or ventricular septal defects and 4 control patients had tests performed in both the pulmonary artery and right ventricle in the course of the same catheterization. The 2 ratios were within 10 per cent of each other in 21 of the 25 patients, and within 6 per cent of each other in 17 patients. It was of interest that relatively well-mixed blood was obtained in the right ventricular outflow tract in patients with ventricular septal defect; 9 of 12 such patients had right ventricle ratios within 5 per cent of their pulmonary artery ratios.

Discussion

The inhalation of 50 per cent N_2O for short periods of time is relatively innocuous. Occasionally a patient experiences slight dizziness after the test, but this is transient. The advantages of this high concentration is that a larger arteriovenous difference is achieved, rendering technical and analytic errors of less importance. Among cyanotic patients, for example, adequate arterial levels were virtually always achieved with 50 per cent N_2O, while more than half of the tests previously done with 15 per cent N_2O were considered unsatisfactory because of low arterial levels.

The need of an earlier sampling period became apparent as increasing numbers of infants and children were studied. In these patients the circulation time is much shorter than in adults with rheumatic heart disease. In children arterial saturation with N_2O was frequently complete within 30 seconds, and the venous level often rose to 25 or 35 per cent of the arterial level by the end of the first

minute of inhalation (fig. 2). It therefore became necessary to determine an earlier sampling period during which the venous level in patients with rapid circulation times would still approximate zero, and yet the arterial level in patients with slow circulation times would be adequate. A study of different sampling periods resulted in the selection of an integrated sample drawn between the tenth and thirtieth seconds of inhalation. This technique yielded satisfactory tests in more than 95 per cent of patients studied. In an occasional patient with an exceptionally long circulation time, it is necessary to use a later sampling interval, such as 30 to 50 seconds. It should be noted that chronic lung disease with impairment of pulmonary diffusion may also be responsible for a low arterial level.

With the earlier sampling period the venous content never exceeded 15 per cent and was usually less than 10 per cent of the arterial content in control patients. With the original 1-minute sampling period, levels as high as 20 per cent in the pulmonary artery and 30 per cent in the right atrium were observed in control patients. This difference between chambers has not been observed in the present study and the same diagnostic criteria may now be applied to tests performed in all 3 areas. On the basis of the 150 tests summarized in figure 3, it is now considered that the diagnosis of a shunt can be made when the right heart or pulmonary artery level is 20 per cent or more of the arterial level. The absence of a shunt is assured by a venous level less than 15 per cent of the arterial level. Tests between 15 and 20 per cent are equivocal and should be repeated.

It is not difficult to detect large left-to-right shunts by the demonstration of a difference in O_2 content of blood sampled from the venae cavae, right heart, and pulmonary artery. However, with small shunts this method is limited by the magnitude of the systemic arteriovenous O_2 difference. To produce an increase in O_2 content of 1.0 vol. per cent distal to a shunt, the flow through the shunt must be at least 33 per cent of systemic flow when the systemic arteriovenous difference is 4.0 vol. per cent. If the systemic arteriovenous difference is 8.0 vol. per cent, the flow through the shunt need only be 17 per cent of systemic flow to produce the same increase in O_2 content. Thus, the sensitivity of the O_2 method is directly proportional to the magnitude of the systemic arteriovenous difference. The sensitivity of the N_2O test, on the other hand, is not altered by the large range of arteriovenous differences in N_2O content. Although the highest arterial N_2O level in this series was 7 times larger than the lowest arterial level, and the resulting arteriovenous differences were similarly distributed, this variation was equalized by expressing the venous levels as percentages of the corresponding arterial levels. Shunts less than 15 per cent of systemic flow could uniformly be detected with the N_2O test (fig. 5).

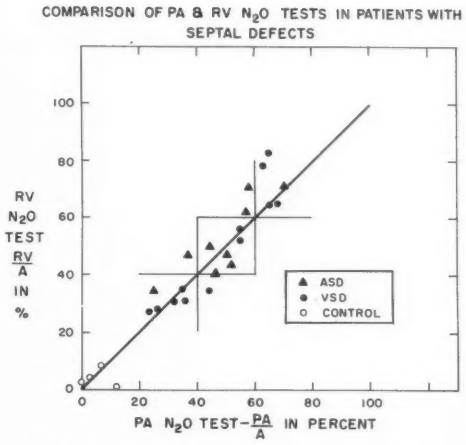

FIG. 6. The reproducibility of repeat N_2O tests in the right ventricle and pulmonary artery of 25 patients. The solid diagonal line indicates the points where the 2 tests were the same. The boxed-in area includes the ratios between 40 and 60 per cent.

Calculations of the magnitude of left-to-right shunts from the systemic and pulmonary arteriovenous O_2 differences have long been recognized to be little better than estimates and subject to considerable error.[14] The inaccuracies of the method are due in part to the difficulty in obtaining a representative mixed venous sample proximal to the shunt, particularly when caval sampling is necessary in

shunts at the atrial level. A larger source of error is introduced as the pulmonary arteriovenous difference approaches 1.0 vol. per cent. In this range, the small analytic errors in determining the O_2 content of the 2 blood samples can assume very large proportions. This may well be the explanation for pulmonary flows sometimes calculated to be as high as 10 or 15 times systemic flow. The fact that the calculations derived from the N_2O test demonstrated only 1 pulmonary flow: systemic flow ratio in excess of 3:1 would support this hypothesis.

However, the calculation of the size of a shunt from N_2O data is also subject to criticism. The arteriovenous difference in N_2O content is rapidly changing throughout the test, and the rise in N_2O content of peripheral arterial blood lags behind that of shunted blood by the circulation time between the left heart and the peripheral artery used for sampling. The use of integrated blood samples averages the changing levels and the dead space in the catheter tends to compensate for the circulation time delay. It is anticipated that comparison of the N_2O and O_2 methods in experimental animals with metered flows will indicate the accuracy of each technic. Such studies are now in progress. In terms of clinical evaluation and preoperative selection of patients, shunts need only to be considered as small, medium, or large. The N_2O ratios provide a convenient means for such a classification. A pulmonary artery test between 40 and 60 per cent indicates a moderate-sized shunt, estimated to produce a pulmonary to systemic flow ratio of 1.5 to 2.5:1 (fig. 4). Pulmonary arterial N_2O tests of 20 to 40 per cent indicate relatively small shunts, and ratios over 60 per cent are associated with large shunts. The 21 patients with atrial and ventricular septal defects represented in figure 6 are so divided according to the size of their shunts. The reproducibility of the test is shown by the fact that in 17 of 21 repeat tests a given patient's classification was not changed.

Summary

The localization of left-to-right circulatory shunts by the nitrous oxide test has been facilitated by modifications of the original technic. In the course of right heart catheterization, patients inhaled 50 per cent N_2O for 30 seconds as integrated blood samples were drawn simultaneously from the pulmonary artery or right heart and a systemic artery. In 78 tests performed in patients without shunts, the N_2O content of blood from the right atrium, right ventricle, or pulmonary artery was always less than 15 per cent of the arterial content. Among 72 tests carried out in patients with left-to-right shunts the venous sample exceeded 20 per cent of the corresponding arterial sample in all but 2 instances.

The magnitude of a left-to-right shunt could be calculated from the results of the N_2O test by the application of a formula relating systemic and pulmonary N_2O arteriovenous differences. A simpler estimate of the shunt could be made directly from the N_2O ratio: small shunts gave ratios of 20 to 40 per cent; intermediate shunts with pulmonary to systemic flow ratios of 1.5 to 2.5:1 gave ratios of 40 to 60 per cent; large shunts were associated with N_2O ratios exceeding 60 per cent. In 43 patients the N_2O test was compared with the method of O_2 differences. It was found that with the N_2O test, shunts comprising less than 15 per cent of the pulmonary flow could uniformly be detected, while with the O_2 method, shunts 25 per cent of the pulmonary flow often escaped recognition.

Summario in Interlingua

Le localisation de sinistro-dextere derivationes circulatori per medio del test a oxydo nitrose pote esser simplificate per modificationes del technica original. In le curso de catheterismo dextero-cardiac, le patientes inhala 50 pro cento de oxydo nitrose durante 30 secundas, e simultaneemente specimens de sanguine integrate es prendite ab le arteria pulmonar o ab le corde dextere e ab un arteria systemic. In 78 tests in patientes sin derivation, le contento de oxydo nitrose in specimens de sanguine ab le atrio dextere, le ventriculo dextere, o le arteria pulmonar esseva semper minus que 15 pro cento del contento de oxydo nitrose in specimens de sanguine arterial.

In 72 tests effectuate in patientes con derivationes sinistro-dextere, le specimen venose monstrava un contento de oxydo nitrose de plus que 20 pro cento del contento arterial de oxydo nitrose in omne casos con 2 exceptiones. Le magnitude del derivation sinistro-dextere poteva esser calculate ab le resultatos del test a oxydo nitrose per le application de un formula que interrelationa le systemic con le pulmonar differentias arterio-venose de oxydo nitrose. Un plus simple estimation del derivation pote esser facite directemente super le base del proportion de oxydo nitrose. Micre derivationes monstrava proportiones de 20 a 40 pro cento. Derivationes de magnitudes intermediari (con proportiones inter fluxo pulmonar e fluxo systemic de inter 1,5 e 2,5 a 1) monstrava proportiones de 40 a 60 pro cento. Grande derivationes esseva associate con proportiones de plus que 60 pro cento. In 43 patientes le test a oxydo nitrose esseva comparate con le methodo a differentias de O_2. Esseva constatate que le test a oxydo nitrose esseva uniformemente capace a deteger derivationes amontante a minus que 15 pro cento del fluxo pulmonar. Del altere latere, le methodo a O_2 resultava frequentemente in le non-detection de derivationes amontante a 25 pro cento del fluxo pulmonar.

REFERENCES

1. Morrow, A. G., Sanders, R. J., and Braunwald, E.: The nitrous oxide test: An improved method for the detection of left-to-right shunts. Circulation **17**: 284, 1958.
2. Callaway, J. J.: Unpublished experimental data.
3. Morrow, A. G., Braunwald, E., Haller, J. A., and Sharp, E. H.: Left heart catheterization by the transbronchial route: Technic and applications in physiologic and diagnostic investigations. Circulation **16**: 1033, 1957.
4. Swan, H. J. C., and Wood, E. H.: Symposium on diagnostic applications of indicator-dilution technics: Localization of left-to-right shunts. Proc. Staff Meet., Mayo Clin. **32**: 486, 1957.
5. Braunwald, E., Tannenbaum, H. L., and Morrow, A. G.: Dye dilution curves from left heart and aorta for localization of left-to-right shunts and detection of valvular insufficiency. Proc. Soc. Exper. Biol. & Med. **94**: 510, 1957.
6. —, —, and —: Localization of left-to-right cardiac shunts by dye-dilution curve following injection into the left heart and aorta. Am. J. Med. **24**: 203, 1958.
7. Grant, R. R., Sanders, R. J., Morrow, A. G., and Braunwald, E.: Symposium on diagnostic methods in the study of left-to-right shunts. Circulation **16**: 791, 1957.
8. Hilbish, T., and Morrow, A. G.: Why selective angiography? Radiology. In press.
9. Kety, S. S.: Quantitative determination of cerebral blood flow in man. Meth. Med. Res. **1**: 204, 1950.
10. Van Slyke, D. D., and McNeill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. J. Biol. Chem. **61**: 323, 1924.
11. Cary, H. H., and Beckman, A. O.: A quartz photoelectric spectrophotometer. J. Optic. Soc. America **31**: 682, 1941.
12. Booth, E. T.: Personal communication.
13. Eppinger, E. C., Burwell, C. S., and Gross, R. E.: The effects of the patent ductus arteriosus on the circulation. J. Clin. Invest. **20**: 127, 1941.
14. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Seibel, R. E., and Evans, J. M.: Studies of congenital heart disease. I. J. Clin. Invest. **26**: 547, 1947.

The Clinical Measurement of Retinal Arterial Pressure

By RICHARD B. PERRY, M.D., AND JOHN C. ROSE, M.D.

The determination of retinal diastolic arterial pressure by ophthalmodynamometry is described. In both normal and hypertensive subjects there was an average difference of 20 mm. Hg between retinal and brachial arterial diastolic pressures. The clinical usefulness of this procedure was demonstrated in patients with obstructive lesions in the internal carotid artery.

THE importance of the retinal blood vessels in physical diagnosis has always been emphasized. However, it is only in recent years that physicians have appreciated a simple technic for measuring the pressure within these vessels. "Ophthalmodynamometry" is the determination of retinal artery pressure by application of a measured external force to the sclera, combined with ophthalmoscopic visualization of the retinal vessels. In effect, the eyeball is used as a sphygmomanometer, collapsing the retinal artery when increasing intraocular tension exceeds the intravascular pressure.

The ophthalmodynamometer currently in use was designed by Bailliart in 1917,[1, 2] but for many years it was of interest only to ophthalmologists.[3–12] Increasing recognition of the syndrome of thrombosis of the internal carotid artery[13–17] and the observation that ophthalmodynamometry is a useful tool in the diagnosis of this disorder[18–22] has now brought this procedure to the attention of internists, neurologists, and neurosurgeons.

This paper deals with a general evaluation of this measurement. First, the relationship of retinal arterial diastolic pressure to brachial arterial diastolic pressure was explored. Second, the significance of factors that purport to correct for varying intraocular tensions was studied. Finally, the clinical usefulness of this procedure in the study of patients with neurologic vascular disease was confirmed.

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MATERIALS AND METHODS

The subjects examined were 31 healthy adults with normal systemic arterial pressures, 44 adults with varying degrees of systemic arterial hypertension (brachial diastolic pressure above 90 mm. Hg plus retinal vascular changes signifying hypertension), and 37 patients with evidences of neurologic vascular disease. All measurements of blood pressure and intraocular tension were performed by one observer.

In normal subjects and hypertensive patients, the blood pressure was measured on one arm by the auscultatory method with a standard sphygmomanometer. When necessary for careful observation, the pupils were dilated with 0.5 per cent hydroxyamphetamine (Paredrine) solution. The external eye was anesthetized with 0.5 per cent tetracaine. With the subject supine, intraocular tension was then measured bilaterally with the Schiotz tonometer. *Diastolic* retinal arterial pressure was determined bilaterally. The blood pressure cuff measurement was then repeated on the opposite arm. Retinal vascular alterations were evaluated for hypertension and arteriolosclerosis by the criteria of Leishman[23] and Wagener and Keith.[24]

The same procedure was followed in 4 patients while the systemic arterial pressure was continually monitored via an indwelling femoral arterial needle, a strain-gage transducer, and a direct-writing recorder.

In the 37 patients with neurologic disease, retinal *diastolic* pressure measurements were obtained in the same manner, the same agents being used when necessary for dilatation of the pupils and local anesthesia. Thirteen of these patients had either differences between right and left eyes of over 15 per cent in the retinal diastolic pressure measurements, or clinical states suggestive of internal carotid artery thrombosis. These 13 subsequently had carotid arteriograms.

The Bailliart ophthalmodynamometer[6] consists of a spring-loaded plunger within a sliding barrel. The plunger is calibrated to indicate pressure in the range of 20 to 150 Gm. water. The instrument and the technic for its use have been illustrated in recent publications.[7, 19-21] Calibrations were made periodically throughout the present study.

With the patient supine, the slightly convex metal foot plate was applied horizontally to the lateral surface of the sclera at the point of insertion of the lateral rectus muscle. By direct ophthalmoscopy the observer's attention was focused on the arteries overlying the optic disk and simultaneously the ophthalmodynamometer was pressed against the eyeball. When the intraocular tension attained the level of the retinal arterial diastolic pressure, the artery on the disk was noted to pulsate maximally. At this point, a convenient brake was applied to the plunger and the instrument was withdrawn from the eye in order to record the reading reached on the plunger scale.

The retinal *veins* are often noted to pulsate at an intraocular pressure lower than the retinal arterial diastolic pressure. These pulsations can be distinguished by the appearance of the veins themselves and their lack of abruptness as compared to arterial pulses. The retinal arteries may be noted to pulsate slightly, prior to attaining the diastolic pressure. These pulsations can be noted in an estimated one third of all normal subjects by standard direct ophthalmoscopy, and in all patients by specialized[2,3] ophthalmoscopes. However, this small expansile movement becomes a well defined collapsing pulse when the intraocular tension equals or exceeds the retinal arterial pressure.)

Systolic retinal arterial pressure may be measured by applying pressure to the sclera until visible arterial pulsations cease and the retinal arteries are blanched. This magnitude of intraocular tension causes transient ocular hypotonia, so that accurate measurements can be made at no less than half-hour intervals. Diastolic measurements may be repeated several times in quick succession without significantly affecting the result. Systolic measurements were not made in the present study. It is generally agreed that diastolic measurements proved sharper and more reproducible endpoints.[2, 7, 29] Further, in hypertensive patients, the systolic pressure in the retinal vessels often exceeds the upper limit of the standard ophthalmodynamometer scale.

The conversion scale of Magitot and Bailliart[6] was used to convert the tension applied to the sclera into standard blood pressure units (mm. Hg). This conversion is based on the intraocular tension measurement obtained with the Schiotz tonometer. The necessity for this conversion was evaluated in the present study.

[6] Obtained from E. B. Meyrowitz Company, New York, N. Y.

Results

Correction Factors. In 75 subjects with normal intraocular tensions (but with or without arterial hypertension) the uncorrected retinal artery pressure ranged from 24 to 144 Gm. When corrected for intraocular pressure by the conversion scale of Magitot and Bailliart, the range was from 25 to 140 mm. Hg. The mean uncorrected pressure was 76.4 and the mean corrected pressure 76.8. The difference was not significant.

The normal intraocular tension was taken as a tonometric reading below 24 mm. Hg. The range in the subjects in this series was 10 to 24 mm. Hg. Only 1 subject with normal intraocular pressure showed a retinal artery pressure measurement slightly in excess of the brachial artery pressure (3 mm. Hg). The correction factor in this instance reduced the retinal artery pressure to 2 mm. Hg below brachial artery pressure. (One patient had a tonometric reading of 24.4 mm. Hg. This patient was subsequently found to have glaucoma and is *not* included in the present series. The uncorrected retinal artery pressure was 73 per cent of the brachial artery pressure. In this case, the correction factor raised the retinal artery measurement to 96 per cent of the brachial artery pressure.)

In view of the generally insignificant effect of correction factors in subjects with normal intraocular tension, the following analyses are confined to *uncorrected* retinal artery pressure measurements.

Ratio of Retinal Artery to Brachial Artery Pressure. Retinal artery pressure measurements taken in the right and left eye were averaged. In 75 patients with brachial diastolic pressures ranging from 49 to 160 mm. Hg, retinal artery pressures ranged from 24 to 144 Gm. (mm. Hg).

Relationships between brachial and retinal artery pressures are summarized in figure 1. In this figure, data are ranked according to each 10-mm.-Hg increment in retinal artery

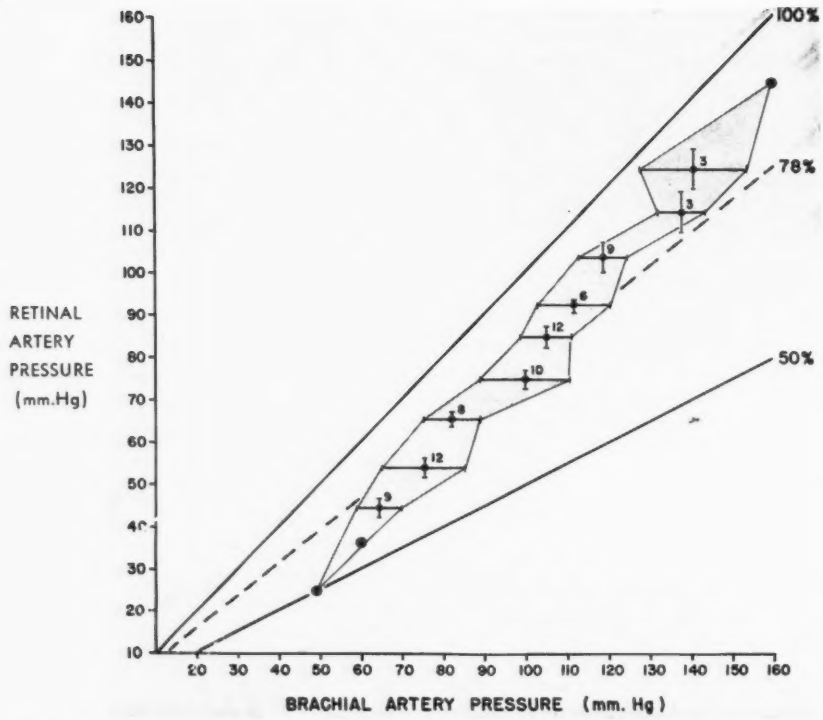

FIG. 1. Relationship of diastolic retinal artery to diastolic brachial artery pressure in 75 patients. Data are ranked according to each 10-mm.-Hg increment in retinal artery pressure between 40 to 129 mm. Hg. Points outside this range (2 below, 1 above) are single cases. Standard deviations are indicated. Numbers of cases are shown within the shaded area.

pressure between 40 to 129 mm. Hg. *Mean* differences between retinal and brachial artery pressures are shown with their standard deviations. For example, in the retinal artery pressure range of 60 to 69 mm. Hg (8 cases) the brachial pressure averaged 16.6 mm. Hg higher (S.D. ± 7.0); in the retinal artery pressure range 90 to 99 mm. Hg (6 cases) the brachial artery pressure averaged 19.8 mm. Hg higher (S.D. ± 8.8).

The retinal artery pressure averaged 78 per cent of the brachial artery pressure for the entire group. However, figure 1 reveals that the observations do not fall parallel to the 78 percentile line, but are less in normotensive subjects and greater than 78 per cent in hypertensive patients. Absolute differences between retinal and brachial diastolic pressures averaged 20.4 mm. Hg. Figure 1 reveals this to be a closer correlation between the 2 pressures, since the group of determinations is parallel to the 100 percentile line.

In an attempt to arrive at closer correlations, the individual observations were divided into 2 groups with a brachial artery pressure of 90 mm. Hg as the dividing line. In individual subjects with brachial artery pressures below 90 mm. Hg, the retinal artery pressure averaged 73 per cent of the brachial artery pressure (S.D. ± 10). In subjects with brachial artery pressures above 90 mm. Hg, the retinal artery pressure averaged 81 per cent of the brachial artery pressure (S.D. ± 9). In the normotensive group, the mean absolute difference between brachial and retinal diastolic pressures was 19.5 mm. Hg (S.D. ± 7). In the hypertensive group, this difference averaged 21 mm. Hg (S.D. ± 10).

D *ferences in Retinal Artery Pressure Between Left Eye and Right Eye.* In the 75 sub, ts with average retinal artery diastolic pre ures between 24 and 144 mm. Hg, the diff ence between right eye and left eye ran d between zero and 14 per cent. The mea difference was 2.3 mm. Hg or 3 per cent. In subjects, there was no difference between rig and left retinal artery pressure.

O hthalmodynamometry with Simultaneous Dir t Intraarterial Pressure Recordings. The app cation of the ophthalmodynamometer to the clera did not significantly alter systemic art ial pressure. Omission of local anesthesia id not alter the tracings. One patient wit frequent extrasystoles showed an increased frequency of ectopic beats but no significant change in the continuously monitored femoral arterial pressure.

Study of Patients with Neurologic Vascular Disease. Of 37 patients, 25 had recent sudden onset of hemiparesis. Nine patients had onset of hemiparesis 3 days to 4 years prior to admission. The remaining 3 had recurrent episodes of syncope, blurred vision and aphasia from 1 week to 1 year prior to admission.

Seven of the 37 patients showed a difference of more than 15 per cent between left and right retinal artery diastolic pressures. These differences ranged between 17 and 36 per cent (mean 25 per cent). (In the remaining 30 patients, differences between left and right retinal artery pressures ranged from zero to 14, mean 4 per cent.)

Thirteen of these patients had carotid arteriograms or angiocardiograms including the 7 with retinal diastolic pressure differences of more than 15 per cent. Six arteriograms were entirely negative. These were in the patients with retinal artery diastolic pressure differences of *less* than 15 per cent.

Among the 7 positive x-ray studies 5 carotid arteriograms showed occlusion (3) or marked narrowing (2) of the internal carotid artery on the side of the lower retinal artery pressure. One patient showed a narrow aortic root and ascending arch with no filling of the innominate artery. The left carotid and subclavian arteries appeared relatively normal. The diagnosis of pulseless disease was made. The seventh patient showed normal internal carotid arteries. However, the right anterior cerebral artery was displaced to the left. Marked vascularity was noted in the region of the middle cerebral artery, suggestive of a large tumor in this region. The tumor was demonstrated at craniotomy. In this instance no explanation was evident for the discrepancy between right and left retinal arterial pressures.

The following is a brief description of one of the cases of proven internal carotid artery thrombosis. It demonstrates a relationship of the clinical status to differences between right and left retinal arterial pressure measurements.

A. G. was a 42-year-old man with sudden onset of left-sided headache, right hemiparesis, aphasia, and confusion. His blood pressure was 150/100 and a left Horner's syndrome was demonstrated. Ophthalmodynamometry shortly following admission to the hospital revealed retinal artery pressures of 90 mm. Hg right eye, 75 mm. Hg left eye *(15 per cent difference).* In the 18 hours following admission there was *resolution of the Horner's syndrome and improvement in hemiparesis and aphasia.* With a brachial blood pressure of 120/90, retinal artery pressures were 63 mm. Hg right eye, 62 mm. Hg left eye *(no difference).* Over the next several days, his neurologic status again deteriorated with return of the Horner's syndrome and worsening of right hemiparesis and aphasia. On the ninth day there was a *13 per cent difference* in retinal artery pressures. At that time a left carotid arteriogram showed complete thrombosis of the left internal carotid artery 3 cm. above the bifurcation of the common carotid artery.

Discussion

Several authors have discussed the special anatomic and physiologic features of the retinal circulation with reference to ophthalmodynamometry. Turk has emphasized that retinal vessels behave more like rigid tubes than other vessels because of the high tissue (intraocular) pressures (20 to 25 mm. Hg) to which they are subjected.[10] Duke-Elder[3, 5] and others[6, 10] have suggested that the ophthalmodynamometer measures the lateral pressure of the *ophthalmic artery,* and not of

the vessels viewed on the retina. When these latter vessels are compressed, the blood contained in them is immobilized. The pressure within them then is the lateral pressure of the most proximal arterial branching.

Koch[10] and Duke-Elder[5] listed values for retinal diastolic pressure in normal persons obtained by many authors. Results varied widely. Values obtained in the present series of normotensive subjects (mean 53 mm. Hg) are higher than those obtained by most earlier authors. These discrepancies may result from differences in endpoints, technics, and instruments. In the past 5 years, Bailliart's ophthalmodynamometer has been used almost exclusively. Therefore, more uniformity in measurements by different observers may now be expected. When low diastolic retinal artery pressures were found, Svein and Hollenhorst discovered that these could be elevated by placing the patients supine.[20] This observation has been verified by other authors cited by Koch.[10] (Seven patients in the present series were studied for this effect: sitting pressures averaged 5 mm. Hg lower than those obtained in the supine position.)

The reproducibility of retinal artery pressure measurement was studied by Streiff.[12] With 2 observers working consecutively in 800 patients, the mean error obtained was 2.5 mm. Hg (maximum 7.4 mm. Hg). This accuracy was found to be better than the tonometer.

Measurements published by authors in the past have relied upon the conversion chart of Bailliart and Magitot in converting units from Gm. to mm. Hg. The chart is based upon experiments in anesthetized cats. Furthermore, the gradations are not suitable for precise conversion. The present study indicates that in the range of accuracy of the ophthalmodynamometer, conversion factors are unnecessary in subjects with normal intraocular tensions. The diastolic retinal pressure can be read directly from the instrument.

Bailliart[1, 2] and Koch[10] also noted a progressive increase in the retinal diastolic pressure and in its ratio to brachial diastolic pressure in hypertensive patients. A reason for this changing ratio becomes evident from the observation that absolute differences (mm. Hg) between brachial and retinal arterial pressures are similar in both normotensive and hypertensive groups. Vascular resistance is proportional to a pressure *gradient* divided by blood flow. If one assumes a relative uniformity of blood flow to the eye in all patients, as well as relative uniformity of resistance between the aorta and the eye (composed largely of intraocular pressure), then there must be a relatively uniform pressure gradient from aorta to eye. This gradient is independent of the absolute level of the blood pressure. Therefore, the relationship between brachial and retinal arterial pressures can most accurately be expressed as a difference of approximately 20 mm. Hg. It is less meaningful to express retinal artery pressure as 78 per cent of brachial artery pressure.

The changes in retinal arterial pressures that occur in unilateral obstruction of the internal carotid artery have been described.[18–22] In occlusion of this artery, the decrease of pressure in its various accessible distal branches is proportionate. A significant decrease of retinal artery pressure constitutes a reliable guide to occlusion of the ipsilateral internal carotid artery proximal to the ophthalmic artery.

Thomas and Petrohelos[19] found a reported range of difference in bilateral retinal diastolic pressures of 0 to 14 per cent in approximately 250 subjects without evidence of carotid artery obstruction. Their own average difference between the 2 eyes in 50 normal subjects was 2.7 per cent. They found in the literature 8 cases of internal carotid artery thrombosis with bilateral pressures recorded. These authors added 5 patients and found significant ipsilateral pressure reductions of greater than 15 per cent in all cases. Subsequent authors have confirmed this.[20–22] It is generally agreed that differences from 0 to 14 per cent may be normal, but differences greater than this almost always denote compromised flow through an internal carotid artery. However, the finding of retinal arterial pressure differences in the normal range does not exclude impairment of the internal

carc l blood flow. Borderline difference (10 to 1 per cent), if consistent, warrant an arteri ram when there are neurologic signs. D erences greater than 15 per cent are saic lways to occur in the acute phase of obs ction, but patients have shown gradually creasing pressures in the ipsilateral eye as c ateral flow develops. In these instances digi l pressure over the normal carotid artery owers the pressure in the opposite eye to its vious level.[18, 19]

S eral authors have suggested the clinical usef ness of this technic in selecting patients for arotid ligation and in evaluating the effic ncy of the ligation.[18-20]

Summary

The use of the ophthalmodynamometer as a measure of retinal arterial pressure has been evaluated in 75 subjects with or without systemic hypertension, and 37 subjects with neurologic vascular disease. Direct intraarterial pressure recordings showed no significant alteration of systemic arterial pressure during use of the ophthalmodynamometer.

Correction factors (for conversion to mm. Hg) based on intraocular tension were found unnecessary in subjects with normal intraocular tension. The mean *normal* retinal diastolic arterial pressure was 53.1 mm. Hg and the retinal diastolic to brachial diastolic pressure ratio was 73 per cent (S.D. ± 10). This ratio was increased in hypertensive patients (81 per cent ± 9 in patients with brachial diastolic pressure exceeding 90 mm. Hg). For the whole range of brachial arterial pressures there was an average difference of 20.4 mm Hg between retinal and brachial diastolic pressures. There was no significant alteration in this figure when hypertensive patients were compared with normotensive subjects.

The normal range of difference between eyes was 0 to 14 per cent (mean 2.3 mm. Hg). Differences greater than 15 per cent indicated compromised blood flow through the internal carotid artery on the side of the lower pressure. Seven patients with differences greater than 15 per cent were studied and 6 were found to have obstructing lesions of the internal carotid artery.

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Summario in Interlingua

Le utilitate del ophthalmodynamometro in le mesuration del pression retino-arterial esseva evalutate in 75 subjectos con o sin hypertension systemic e 37 subjectos con morbo vascular neurologic. Directe registrationes del pression intra-arterial monstrava nulle significative alteration del pression arterial systemic durante le uso del ophthalmodynamometro.

In subjectos con normal tensiones intraocular, le introduction de factores de correction super le base del tension intra-ocular (pro le conversion in mm de Hg) se revelava como superflue. Le *normal* valor medie del diastolic pression retino-arterial esseva 53, 1 mm de Hg, e le proportion inter le pression diastolic retinal e le pression diastolic brachial esseva 73 pro cento (con un deviation standard de ±10). Iste proportion esseva augmentate in patientes hypertensive. Illo amontava a 81 pro cento (±9) in patientes in qui le pression diastolic brachial excedeva 90 mm de Hg. Pro le complete scala de pressiones brachio-arterial, le differentia medie inter le diastolic pressiones retinal e brachial amontava a 20 4 mm de Hg. Nulle significative alteration de iste valor esseva constatate in comparar patientes hypertensive con subjectos normotensive.

Le scala del differentias normal inter le duo oculos esseva 0 a 14 pro cento (valor medie 2,3 mm de Hg). Differentias de plus que 15 cento indicava un compromisso del fluxo de sanguine via le interne arteria carotic al latere del pression inferior. Esseva studiate 7 patientes con differentias inter le oculos lesions obstructive del interne arteria carotic amontante a plus que 15 pro cento. In 6, lesiones obstructive del interne arteria carotic esseva constatate.

REFERENCES

1. Magitot, A. P., and Bailliart, P.: Blood pressure in the vessels of the eye. Abstracted, Am. J. Ophth. **5**: 824, 1922.
2. —, and —: How to know the blood pressure in the vessels of the retina. Am. J. Ophth. **5**: 777, 1922.
3. Duke-Elder, W. S.: The ocular circulation: Its normal pressure relationships and their physiological significance. Brit. J. Ophth. **10**: 513, 1926.
4. Bailliart, P.: The Retinal Circulation (translated by J. E. Lebensohn). Chicago, Professional Press, 1928.
5. Duke-Elder, W. S.: Textbook of Ophthalmology. St. Louis, Mosby, 1933.
6. Friedenwald, J. S.: Retinal vascular dynamics, Am. J. Opth. **17**: 387, 1934.
7. Luo, T. H., and Ch'en, H. L.: Ophthalmodynamometric findings in the Chinese. Chinese M. J. **56**: 345, 1939.
8. Constantine, E. F.: A study of the interrelationship of retinal and systemic arterial pressure and intraocular tension in normal and syphilitic patients. Am. J. Ophth. **23**: 436, 1940.
9. Gutmann, A.: Pressure in central artery of retina in allergy with description of a new ophthalmodynamometer. Arch. Ophth. **29**: 457, 1943.
10. Koch, F. L. P.: Ophthalmodynamometry. Arch. Ophth. **34**: 234, 1945.
11. —: Retinal vascular micrometry and essential hypertension. Arch. Ophth. **34**: 321, 1945.
12. Streiff, E. B., and Bischler, V.: The accuracy of ophthalmodynamometry. Ophthalmologica **112**: 19, 1946 (Quart. Rev. Ophth. **4**: 133, 1948).
13. Ochs, L., Sensenbach, W., and Madison, L.: Primary thrombosis of the internal carotid artery. Am. J. Med. **17**: 374, 1954.
14. Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in cerebrovascular disease. V. The use of anticoagulant drugs in the treatment of intermittent insufficiency of the internal carotid arterial system. Proc. Staff Meet., Mayo Clin. **30**: 578, 1955.
15. Sprofkin, B. E., and Blakey, H. H.: Acute spontaneous cerebral vascular accident in young normotensive adults. Arch. Int. Med. **96**: 617, 1956.
16. Van Buskirk, C.: Carotid artery thrombosis. Ann. Int. Med. **45**: 963, 1956.
17. Corday, E., and Rothenberg, S. F.: The clinical aspects of cerebral vascular insufficiency. Ann. Int. Med. **47**: 626, 1957.
18. Miletti, M.: Diagnosis of primary thrombosis of internal carotid in cervical region by determination of values of systolic pressure of the central retinal artery. Presse méd. **54**: 655, 1946.
19. Thomas, M. H., and Petrohelos, M. A.: Diagnostic significance of retinal artery pressure in internal carotid involvement. Am. J. Ophth. **36**: 335, 1953.
20. Svein, H. J., and Hollenhorst, R. W.: Pressure in retinal arteries after ligation or occlusion of the carotid artery. Proc. Staff Meet., Mayo Clin. **31**: 684, 1956.
21. Heyman, A., Karp, H. R., and Bloor, B. M.: Determination of retinal artery pressures in diagnosis of carotid artery occlusion. Neurology **7**: 97, 1957.
22. Wood, F. A., and Toole, J. F.: Carotid artery occlusion and its diagnosis by ophthalmodynamometry. J.A.M.A. **165**: 1264, 1957.
23. Leishman, R.: The eye in general vascular disease. Hypertension and arteriosclerosis. Brit. J. Ophth. **41**: 641, 1957.
24. Wagener, H. P., and Keith, N. M.: Diffuse arteriolar disease with hypertension and the associated retinal lesions. Medicine **18**: 317, 1939.

Patent Ductus Arteriosus with Pulmonary Hypertension Simulating Ventricular Septal Defect

Diagnostic Criteria in Ten Surgically Proven Cases

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The classic findings of a patent ductus arteriosus in a young individual are familiar to most physicians. However, it has been appreciated that several factors, principally pulmonary hypertension or pulmonary artery dilatation in the absence of appreciable hypertension, may significantly alter the classic image and lead to the erroneous diagnosis of ventricular septal defect. In 10 surgically proved cases a patent ductus arteriosus was the sole malformation and so closely simulated a septal defect that extracorporeal circulation was initially considered for each of the patients. Division of the ductus resulted in a complete cure in all 10 patients. Those findings of value in differential diagnosis are analyzed.

THE classic picture of patent ductus arteriosus in a young person, characterized by a continuous murmur, loudest over the pulmonic area, bounding peripheral pulses, increased pulmonary vascular markings, and other radiologic evidences of increased pulmonary blood flow, has become generally familiar. Not infrequently, however, patients carrying this congenital malformation do not conform to the classic syndrome. Several factors change the usual features of the disease, of which pulmonary hypertension is one of the most important. Pulmonary hypertension modifies the shunt so that the diastolic component of the murmur is obliterated and the regurgitation of oxygenated blood through the pulmonary valve may lead to the erroneous diagnosis of high ventricular septal defect. Moreover, pulmonary valvular insufficiency due to a marked dilatation of the pulmonary artery may be secondary to a patent ductus arteriosus with a large left-to-right shunt in the absence of appreciable pulmonary hypertension.

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Among the patients with congenital heart disease who were surgically treated at the University of Minnesota Hospitals between January 1955 and January 1956, 3 children were referred for open cardiac surgery with the diagnosis of ventricular septal defect with pulmonary hypertension. At the time of operation none was found to have intracardiac lesions. Instead, a patent ductus arteriosus was encountered and divided in all. Each of these patients made a complete recovery with total disappearance of their signs and symptoms. It was recognized in retrospect, that these diagnostic errors resulted from the modified clinical picture of the presence of a moderate or severe degree of pulmonary hypertension. After these earlier experiences, 7 similar patients have been correctly diagnosed preoperatively, and successfully treated. The fact that all of these 7 additional patients were referred to us as septal defects after complete study, including cardiac catheterization, has indicated the need for emphasizing the various diagnostic criteria leading to the suspicion of a patent ductus arteriosus as the sole malformation. We have omitted from this discussion those patients having both a patent ductus arteriosus and a septal defect.

It is the purpose of this report to present data (tables 1 to 4) on these 10 patients with patent ductus arteriosus plus pulmonary hypertension and atypical manifestations, all

TABLE 1.—*Physical Findings*

Case no.	Heart size	Thrills	Murmurs	Pulmonic 2nd sound	Blood pressure		Peripheral pulse	Miscellaneous
					Arm	Leg		
1	Enlarged	Absent	Syst. 3rd L.I.S. diast. apex	Accentuated	105/50		Bounding	
2	Enlarged	Absent	Syst. pul. area	Accentuated	95/50	130/70	Normal	Mongoloid high palate
3	Enlarged, precordial bulge	Syst. S.S. notch and L.S.B.	Syst. and diast. pul. area	Accentuated	100/60		Bounding	Bilateral cataracts, deafness
4	Enlarged, precordial bulge	Syst. 3rd L.I.S.	Syst. 3rd L.I.S. diast. apex	Accentuated	130/60	160/70	Bounding	
5	Enlarged	Absent	Syst. along L.S.B.	Accentuated and duplicated	124/60		Strong	
6	Enlarged	Syst. S.S. notch and pul. area	Continuous pul. area	Accentuated and duplicated	140/40/0		Bounding	
7	Enlarged, precordial bulge	Syst. S.S. notch, syst. plus diast. 3rd L.I.S.	Syst. and diast. 3rd L.I.S.	Accentuated and duplicated	124/60/0	160/60/0	Bounding capillary pulse	
8	Enlarged, precordial bulge	Syst. S.S. notch	Continuous pul. area, diast. apex	Accentuated and duplicated	112/35		Bounding	
9	Enlarged, precordial bulge	Syst. S.S. notch and aortic area	Syst. aortic area, diast. pul. area	Accentuated and duplicated	110/60	170/60	Soft fem. right radial stronger than left	
10	Enlarged	Syst. pul. area	Continuous pul. area	Accentuated	95/60	95/65	Normal	

L.S.B. = Left sternal border, L.I.S. = Left intercostal space, S.S. = Suprasternal.

of whom were thought by competent cardiologists to have intracardiac lesions.

REPORT OF CASES

Case 1. This patient's mother had a heart murmur and her mother's sister died during childhood, presumably of a congenital heart defect ("blue baby"). The patient was the product of an uneventful pregnancy and delivery. A rapid heart rate was noted since the first months of life and a heart murmur was detected at the age of 5 months. She subsequently developed easy fatigability and frequent otitis and epistaxis. Cyanosis was never observed.

At the time of admission in January 1955 she was 6 years old, her weight was 18.5 Kg., and her height was 43¾ inches. The heart was moderately enlarged, no thrills were felt, but a grade III sys-

TABLE 2.—*Cardiac Catheterization Data in Ten Patients with Patent Ductus Arteriosus Simulating a Septal Defect (Preoperative)*

	O_2 Content (vol. %)								Pressure, mm. Hg					
	Sup. Cava	Inf. Cava	R.A.	R.V.	P.A.	Aorta	Brach. Art.	Fem. Art.	R.A.	R.V.	Pul. Art.	Aorta	Brach. Art.	Fem. Art.
	12.50	13.30	11.47	12.77	14.20			16.65 97.3%	3.5/0	80/0	80/49			
	10.23	9.70	10.09	11.22				12.57 91.%		110/0				100/?
	11.90	12.32	11.86	13.05	14.62		15.30 92.5%				66/45		115/45	
	12.19		12.25	14.41	16.64			18.25 94.8%	6/-4	90/0	90/50			135/65
	13.57	13.91	13.96	14.42	16.58			19.04 97.3%	6	89/12	90/45			
	11.70	12.20	11.70	12.90	14.60		15.90 95.%		8/0	65/5	58/36	115/57	130/65	
	12.64	14.76	12.43	14.66	14.98			16.89 98.2%	4/0	60/2.5	38/10			
	8.39	11.68	9.74	13.12	16.98	18.02 102.%			9/5	85/0	85/55	120/75		
	11.0	12.93	11.10	12.96	14.25			15.94 96.7%	9/3	85/0	85/55			
		7.2	7.3	9.3	9.4	10.5		 89.5%	6	40/3	35/23	94/58		

*Case 1 was recatheterized postoperatively. Data showed no shunts and normal pulmonary artery pressure.

tolic murmur was heard along the left sternal border, best at the third and fourth interspaces. A soft apical diastolic murmur was also present. The pulmonary second sound was louder than the aortic second sound and had a snappy quality. The systemic blood pressure was 105/50 mm. Hg and the peripheral arterial pulses were bounding. Roentgenograms were interpreted as showing right ventricular, left ventricular, and left atrial enlargement, prominent and actively pulsating pulmonary artery trunk, increased pulmonary vascular markings, and a small aorta. The electrocardiogram showed left ventricular hypertrophy and left bundle-branch block. Cardiac catheterization in 1954 revealed increases in the oxygen content from the right atrium to the right ventricle to the pulmonary artery and severe pulmonary hypertension (table 2). The most likely diagnostic possibility considered was a ventricular septal defect streaming into the pulmonary artery and severe pulmonary hypertension. The patient was referred to us by the cardiologists for correction of a presumed ventricular defect.

On February 1, 1955, bilateral anterior thoracotomy with transverse division of the sternum was performed. After the pericardium was opened it was obvious that both the aorta and the pulmonary artery were enlarged; a thrill was felt in the pulmonary artery beginning at the site of the pulmonary valve. The diagnosis was of a ventricular septal defect. The child and a donor were heparinized, their venae cavae and systemic arteries were cannulated, and total cardiopulmonary bypass by means of controlled cross circulation[1-4] was accomplished. A right ventricular cardiotomy was performed, and an unusually large flow from the open heart was noted immediately. To dry the operative field, the aorta was temporarily occluded just above the coronary ostia, but the left ventricle became distended. At that time oxygenated blood

TABLE 3.—*Radiologic Findings*

Case no.	Radiographic								Fluoroscopic
	Heart Size	Pulmonary vascularity							
		R.V.	L.V.	L.A.	P.A.	Prox.	Dis.	Aorta	
1	3+	2+	2+	1+	2+	2+	2+	Small*	
2	3+	3+	1+	2+	2+	2+	1+	Small*	
3	2+	2+	1+	N	2+	3+	3+	2+	Pulsatile aorta
4	3+	3+	2+	2+	3+	3+	3+	3+	Pulsatile aorta
5	3+	3+	2+	1+	4+	4+	1+	N*	
6	2+	1+	2+	2+	3+	3+	3+	3+	
7	3+	2+	3+	3+	2+	3+	3+	4+	Very pulsatile aorta
8	3+	2+	2+	2+	2+	2+	2+	N*	
9	2+	1+	2+	1+	1+	1+	1+	N*	Pulsatile aorta
10	3+	3+	N	1+	2+	3+	3+	3+	

*Was enlarged at surgery.
N = Normal
1+ = Mild
2+ = Moderate
3+ = Marked
4+ = Very marked

flowed back from the pulmonary artery into the right ventricle, indicating passage of blood directly from the aorta to the pulmonary artery. As there was no evidence of a ventricular septal defect or of an aortic-pulmonary septal defect, a patent ductus was immediately diagnosed. The cardiotomy was closed and the extracorporeal circuit was interrupted after 7 minutes 41 seconds of perfusion. Then the area of the ductus was dissected, and a large channel measuring 12 to 15 mm. in diameter was found and divided. The thrill in the pulmonary artery disappeared. Other defects were not encountered. A lung biopsy taken at the operation revealed intimal thickening of the small arteries.

The postoperative convalescence was without complication, no heart murmurs could be heard, the systemic blood pressure was 90/60 mm. Hg, and the patient was discharged on March 4, 1955. Six months after surgery roentgenograms revealed a decrease in the size of the heart and the great vessels and normal pulmonary vasculature. At cardiac catheterization no shunt was demonstrated at any level and the pulmonary artery pressure had regained normal values (20/10 mm. Hg).

Case 2. A 6-year-old girl entered the University of Minnesota Hospitals on March 14, 1955, for surgical treatment of a ventricular septal defect. Her mother had been edematous during pregnancy, but no definite pathology was demonstrated. At the age of 5 weeks a diagnosis of mongolism was made and a heart murmur was discovered. Subsequently slow growth rate, retarded development, frequent upper respiratory infections, and episodes of cyanosis were noted. On admission the diagnosis of mongolism was confirmed, her weight was 16.8 Kg., and her height was 40 inches. The heart appeared to be enlarged and a systolic murmur was present in the area of the pulmonary valve. The pulmonary second sound was accentuated. The blood pressure was 95/50 mm. Hg in the arms and 130/70 in the legs. The femoral pulses were easily palpable. Roentgenograph showed considerable cardiomegaly, definite right ventricular enlargement, questionable left ventricular enlargement, and moderate left atrial enlargement. The pulmonary artery segment was prominent, and the central and peripheral pulmonary vasculature was increased. The aorta was considered to be small. The electrocardiogram revealed incomplete right bundle-branch block, prolonged P-R interval, and right ventricular preponderance. Data from a previous cardiac catheterization disclosed an increase in the oxygen content of the right ventricle, the pressure of which was greatly elevated, in fact, greater than the systolic arterial pressure (table 2). Unfortunately the catheter failed to enter the pulmonary artery, so that pressure and oxygen content could not be determined there. The peripheral arterial blood oxygen saturation was slightly diminished, suggesting an associated right-to-left shunt. A diagnosis of ventricular septal defect with severe pulmonary hypertension was made.

On March 21, 1955 the heart and great vessels were exposed by a bilateral transverse thoracotomy in preparation for open cardiotomy. The aorta and the pulmonary artery both appeared enlarged and no thrills were palpated. In view of the large aorta and the experience obtained in case 1, a patent ductus arteriosus rather than a ventricular septal defect was considered. After careful dissection, a large ductus, 15 mm. in diameter, was found. Temporary occlusion of the channel for 15 minutes produced no untoward effects on the heart and circulation; the ductus was then transected. A lung biopsy taken at the operation showed no abnormalities. The postoperative period was uneventful, the only residual physical finding being a very soft systolic murmur in the region of the pulmonic valve. The patient was dismissed from the hospital on April 17, 1955, and has been completely well since.

Case 3. This 6-year-old girl was born from a pregnancy complicated by rubella during the seventh week, and a heart murmur was discovered

at birth. Congenital bilateral cataracts and deafness were found. Slow physical progress, decreased exercise tolerance, frequent upper respiratory infections, and repeated episodes of pneumonitis, characterized her clinical picture.

On admission for surgery on January 6, 1956 she was small and slender; her weight was 14.5 Kg. and her height 43 inches. A precordial bulge was seen, a systolic thrill was easily felt along the left sternal border and the suprasternal notch, a grade III systolic murmur was heard best at the third and fourth left interspaces, and a diastolic murmur was heard in the second left interspace. The pulmonary second sound was accentuated, the blood pressure was 100/60 mm. Hg, and the femoral pulses were bounding. Roentgenograms and fluoroscopy revealed moderate cardiomegaly, mainly of the right ventricle, with slight left ventricular and left atrial enlargement. The pulmonary artery segment was prominent, and pulmonary vascularity was distinctly increased. Likewise, the aorta appeared to be enlarged and actively pulsating. The electrocardiogram showed left ventricular hypertrophy. On cardiac catheterization significant increase in the oxygen content from the right atrium to the right ventricle and a greater increase from the right ventricle to the pulmonary artery were found. A moderate degree of pulmonary hypertension was also observed (table 2). From these data two diagnostic possibilities were considered: a ventricular septal defect with streaming into the pulmonary artery and ventricular septal defect associated with a patent ductus arteriosus. To clarify the diagnosis, a retrograde aortogram via the left subclavian artery with 35 per cent Diodrast was performed. The descending portion of the aortic arch was not completely delineated, but no opacification of the pulmonary arteries was seen. Consequently, a patent ductus arteriosus was not demonstrated. She was then referred for intracardiac correction of a presumed ventricular septal defect.

On January 25, 1956, the chest was entered, as in the previous cases. The heart and the great vessels were enlarged. The aorta pulsated actively and a thrill was felt in the right ventricle. The mean pressures in the pulmonary artery and in the aorta were 36 and 71 mm. Hg respectively. The operation proceeded with the cannulation of the left subclavian artery in preparation for cardiopulmonary bypass. Surprisingly, during these maneuvers the tip of the cannula passed into the pulmonary artery through a ductus, which was then immediately dissected and severed. No thrills could then be felt in the right ventricle or pulmonary artery. A biopsy of the left lung showed arteriolar intimal proliferation. The postoperative course was uncomplicated, all murmurs disappeared, and the blood pressure was 106/80. The patient left the hospital on February 12, 1956. Periodic follow-ups have shown that her exercise tolerance is normal and her growth rate has improved.

TABLE 4.—*Electrocardiographic Findings*

Case no.	Axis	Ventricular hypertrophy	Atrial enlargement	IRBBB	LBBB	Prolonged P-R interval
1	Normal	L			Present	
2	L	R		Present		Present
3	L	L				
4	Normal	R and L		Present		
5	L	R		Present		
6	Normal	L	L			
7	Normal	R and L	L	Present		
8	Normal	L and R				
9	Normal	No definite pattern	L			
10	Normal	R	R			

IRBBB = Incomplete right bundle-branch block
LBBB = Left bundle-branch block

Case 4. This 15-year-old boy was sent from the Philippine Islands for surgical treatment of a ventricular septal defect. He was born after a normal pregnancy. At the age of 1½ years he had a urinary tract infection and anasarca, which apparently responded well to medical management. A heart murmur was first heard at the age of 2½ years. A definite decrease in exercise tolerance and repeated episodes of respiratory infections and pneumonia have characterized his disease. Cardiac catheterization in his home country showed a left-to-right shunt of 4.7 volumes per cent at the ventricular level, with pulmonary hypertension.

On August 8, 1956, physical examination disclosed a prominent precordial region and a large heart. A systolic thrill and a grade IV systolic murmur in the third left intercostal space were noted. In addition, there were a faint apical diastolic murmur and an accentuated pulmonary second sound. The blood pressure in the arm was 130/60 and in the leg 160/70. The femoral arteries pulsated widely. Salient radiologic features were a marked cardiomegaly with predominant right ventricular and left atrial enlargement. The pulmonary vasculature was increased and both the aorta and the pulmonary artery were enlarged and actively pulsating. The electrocardiogram showed biventricular hypertrophy and incomplete right bundle-branch block. Cardiac catheterization at this time revealed a left-to-right shunt at the

level of the right ventricle and pulmonary artery, as well as severe pulmonary hypertension (table 2).

On the basis of these data a preoperative diagnosis of a patent ductus was made, and the chest was entered through a left thoracotomy. A large short ductus, 20 mm. in diameter, was found. At this point a 0.1 per cent solution of trimethaphan camphorsulfonate (Arfonad) in 5 per cent dextrose in water was slowly administered intravenously, lowering the systemic blood pressure from 110 to 70 mm. Hg. This reduction of the pressure in the great vessels and the ductus itself considerably facilitated division of the ductus.

The patient's postoperative course was uncomplicated, his general condition gradually improved, and he became completely normal 1 year after the operation. No residual murmurs remain.

Case 5. This 20-year-old woman entered the University of Minnesota Hospitals from a medical center in Southern United States with a diagnosis of an atrial septal defect or atrioventricularis communis, based on cardiac evaluation including heart catheterization. She was the product of a normal pregnancy and delivery. From the first year of life she had increasing dyspnea on mild exertion. A heart murmur was heard for the first time at the age of 4 years.

On July 29, 1956 she was a short, obese, white woman weighing 59.5 Kg. Physical examination showed that the heart was enlarged. A grade II systolic murmur was heard along the left sternal border, and the pulmonary second sound was duplicated and greatly accentuated. The blood pressure was 124/60 and the femoral pulses were easily palpated. Roentgenograms revealed marked cardiomegaly with biventricular enlargement, the left atrium being only slightly prominent. The pulmonary artery trunk and the central pulmonary vessels were hugely dilated, whereas the peripheral pulmonary vasculature was only slightly increased. The aorta was of normal or slightly diminished size. The electrocardiogram showed left axis deviation, incomplete right bundle-branch block, and right ventricular hypertrophy. Cardiac catheterization was repeated; a left-to-right shunt at the level of the pulmonary artery and a marked elevation of the pulmonary artery pressure were encountered (table 2). Although the diagnosis of a patent ductus arteriosus seemed obvious, a retrograde aortogram through the left subelavian artery was carried out for confirmation. This study demonstrated simultaneous opacification of the distal aortic arch and the pulmonary vessels. In addition, a ductus diverticulum was also suggested.

On August 13, 1956 a patent ductus arteriosus, 15 mm. in diameter, was found and divided while the blood pressure was lowered from 140 to 60 mm. Hg with the administration of intravenous Arfonad. The patient did well after surgery and no residual murmurs could be heard. She was discharged on August 25, 1956.

Case 6. This 13-year-old girl had been considered healthy until the age of 8 years, when a heart murmur was discovered during a routine physical examination and a patent ductus was diagnosed. In 1952 she was surgically explored in her home country of Brazil but no ductus arteriosus was found. A second catheterization in Brazil revealed pulmonary hypertension, a left-to-right shunt at the ventricular level and a left-to-right shunt at the pulmonary artery level. In addition, the catheter was passed from the pulmonary artery into the aorta. The catheterization report stated that the catheter passed through an aortic septal defect rather than through a patent ductus (no films were taken). Therefore, a diagnosis of an aortic septal defect plus pulmonary valve insufficiency, or an aortic septal defect plus a high ventricular septal defect, was considered. The patient was then sent to us for corrective surgery by means of cardiopulmonary bypass.

On admission, April 23, 1957, physical examination showed her to be a rather slender girl with an enlarged heart and forcible cardiac impulse. A systolic thrill in the upper left sternal border and the suprasternal notch, and a grade III continuous murmur in the pulmonary valve area, were observed. The pulmonary second sound was duplicated and accentuated, the blood pressure was 140/40/0, and the peripheral arterial pulsations were bounding. Radiologic examination showed moderate cardiomegaly, bilateral but predominant left ventricular enlargement, and left atrial enlargement. Both the aorta and the pulmonary artery appeared to be distinctly enlarged and the pulmonary vasculature was engorged. The electrocardiogram revealed left atrial and marked left ventricular hypertrophy. The reported findings on catheterization and thoracotomy seemed so definite that no further special diagnostic studies were carried out by us.

On April 26, 1957 the chest was opened through a bilateral anterior transverse thoracotomy with the pump-oxygenator setup. When the pericardium was opened, no abnormality was found at the root of the great vessels. The area of the ductus was then explored. A large channel was identified, dissected and divided. Arfonad was used to induce hypotension, lowering the systolic blood pressure from 140 to 85 mm. Hg during the clamping of the ductus.

Except for pleural effusion promptly controlled by routine measures there were no postoperative complications. All murmurs disappeared and the blood pressure regained values of 120/85 mm. Hg. The patient was dismissed from the hospital 17 days after surgery.

ase 7. This 11-year-old boy, apparently nor-m , was first known to have a heart murmur dur-in a routine physical examination in October 1 5. Subsequently a slight decrease in exercise t rance was also noted. In May 1956, appen-d tomy was performed. He was admitted to the U iversity of Minnesota Hospitals in October 1 6, at which time cardiac catheterization was p formed (table 2). A diagnosis of ruptured a urysm of the sinus of Valsalva into the right v ntricle was made and he was scheduled for e racorporeal circulation.

The patient was readmitted on August 20, 1957, f r intracardiac surgery. Physical examination r vealed an enlarged heart, a systolic thrill in the s prasternal notch, and a systolic and diastolic thrill along the left sternal border. On auscultation a grade IV systolic and diastolic murmur was heard in the third left interspace transmitted to the neck and back. The pulmonic second sound was accentuated and duplicated. The blood pressure was 124/60/0 in the arm and 160/60/0 in the leg. A Corrigan type of femoral pulses and a capillary pulse in the nailbeds were observed. Salient radiologic features were marked cardiomegaly, mainly from left ventricular and left atrial enlargement, moderate prominence of the pulmonary artery trunk, and distinct engorgement of the pulmonary vessels. The aorta was massively enlarged and widely pulsatile (fig. 1). The electrocardiogram showed left atrial hypertrophy, incomplete right bundle-branch block, and biventricular hypertrophy. Previous cardiac catheterization had disclosed a left-to-right shunt at the ventricular level and pulmonary hypertension.

At this admission, in the light of the increased experience, several diagnoses were proposed. These were a ruptured sinus of Valsalva aneurysm into the right ventricle, a ventricular septal defect together with aortic regurgitation, or a patent ductus arteriosus associated with pulmonary valve insufficiency. For a clarification of the diagnosis, an aortogram by a catheter inserted retrogradely into the aorta from the left brachial artery was scheduled. The catheter was passed up the aortic arch, and then it was seen to enter the pulmonary artery and the right ventricle. Films taken at this time showed that the catheter had passed through a ductus rather than an aortic-pulmonary septal defect. While the catheter was slowly withdrawn from the right ventricle to the aorta the pressure in the right ventricle was 70/0 mm. Hg, in the pulmonary artery, 70/35 mm. Hg, and in the aorta, 110/70 mm. Hg. Thus injection of contrast material was not deemed necessary.

At operation on August 29, 1957, a large ductus measuring 15 mm. in diameter was found. There was a marked thrill in the pulmonary artery that disappeared on occlusion of the ductus, at which time the blood pressure increased 40 mm. Hg. Induced hypotension with Arfonad lowered the pressure from 160 to 100 mm. Hg. The ductus was then divided.

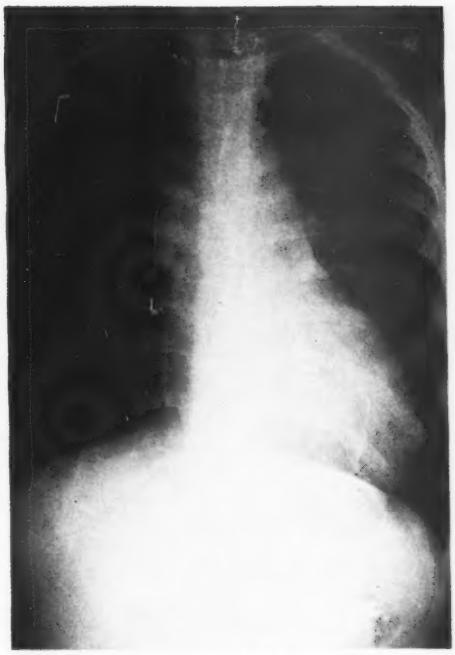

FIG. 1. Roentgenogram (posteroanterior view), of a patient (case 7) with patent ductus arteriosus simulating intracardiac shunt. At catheterization a left-to-right shunt with pulmonary hypertension was identified at ventricular level. Note enlarged ascending aorta and aortic arch, suggesting patent ductus arteriosus.

A lower-left pneumonia complicated the postoperative course but responded well to medical treatment. The patient left the hospital 16 days after surgery, at which time no murmurs were heard.

Case 8. This 4-year-old girl was the product of an uncomplicated pregnancy and delivery. Frequent upper respiratory infections since early life, one episode of pneumonia, and a rapid respiratory rate were reported. A heart murmur was discovered at the age of 2 months. One episode of purpura was adequately controlled. A retrograde aortogram via the left brachial artery taken in 1953 failed to demonstrate a ductus arteriosus. On cardiac catheterization in 1955, a diagnosis of patent ductus arteriosus was established by passing the catheter through it into the descending aorta. However, in addition to a left-to-right shunt at the level of the pulmonary artery, a left-to-right shunt at the ventricular level was

FIG. 2. Retrograde aortography, (anteroposterior view), case 9. Simultaneous opacification of aorta and pulmonary arteries.

also encountered. Severe pulmonary hypertension was likewise demonstrated. Two diagnostic possibilities were then taken into consideration: a patent ductus arteriosus plus a ventricular septal defect; a patent ductus arteriosus plus pulmonary valvular insufficiency as a result of pulmonary hypertension.

Physical examination on September 15, 1957 revealed a fairly well developed child with a precordial bulge and active precordium. A systolic thrill was felt in the suprasternal notch, and a continuous machinery-like murmur was heard in the pulmonary valve area. In addition, there was an apical diastolic rumbling and the pulmonary second sound was accentuated and duplicated. The blood pressure was 135/35 mm. Hg and the femoral pulses were bounding. Her weight was 16.3 Kg. and her height was 40¾ inches. Roentgenograms revealed considerable cardiomegaly, with enlargement of both ventricles and the left atrium. The pulmonary artery trunk was dilated and the pulmonary vascular markings were increased. The aorta appeared normal or relatively small. The electrocardiogram showed left and right ventricular hypertrophy and strain.

The left thorax was opened on September 17, 1957, and a large ductus arteriosus was found. A prominent thrill in the pulmonary artery disappeared upon occlusion and division of the ductus. A lung biopsy obtained at surgery demonstrated only chronic passive hyperemia.

The postoperative course was satisfactory. A grade I systolic murmur at the pulmonic area remained as the only physical finding. The blood pressure was 108/75 mm. Hg. The patient was discharged 2 weeks after the operation.

Case 9. This twin 8-year-old girl was the product of an otherwise normal pregnancy. Her birth weight was 3 pounds, 7 ounces. When she was 3 months old rapid respiration was noted and a heart murmur was discovered. Subsequently, increasing dyspnea on exertion and frequent respiratory infections became apparent. At the age of 7 years she developed an episode of acute nephritis. Her twin sister was known to have had no illnesses.

The patient's cardiovascular condition was evaluated by several means, including cardiac catheterization, at a university hospital in southwestern United States. She was admitted to the University of Minnesota Hospitals on September 16, 1957, for surgical treatment with the diagnosis of ventricular septal defect. Her weight was 17.2 Kg. and her height was 47 inches. Physical examination showed a short, slender girl with a precordial bulge and a systolic thrill in the suprasternal notch and in the second right interspace. A grade IV systolic murmur was heard best at the second right interspace and a short diastolic murmur was heard at the upper left sternal border. The pulmonic second sound was accentuated and duplicated. The blood pressure was 110/60 mm. Hg in the right arm, 100/60 in the left arm, and 70/60 in the lower extremities. The right radial pulse was stronger than the left, and the femoral pulses were soft although easily palpable. Roentgenograms indicated moderate cardiomegaly with predominant left ventricular and left atrial enlargement. The pulmonary artery and the pulmonary vasculature were slightly prominent. On fluoroscopy the aorta was normal in size but pulsated with increased amplitude. The electrocardiogram showed left atrial hypertrophy but no definite ventricular hypertrophy. Cardiac catheterization performed at this time disclosed similar results to those obtained elsewhere. There was a left-to-right shunt at the ventricular level, a left-to-right shunt at the pulmonary artery level, and severe pulmonary hypertension. Two diagnostic explanations were offered: a patent ductus arteriosus plus a ventricular septal defect, or patent ductus arteriosus plus pulmonary regurgitation. Coarctation of the aorta associated with an aortic valve abnormality was also considered a possible condition. A retrograde aortogram via the left subclavian artery showed simultaneous opacification of the aortic arch and large pulmonary arteries,

and large ductus arteriosus and a distinct narrowing of the aorta at the level of the ductus were visualized (figs. 2 and 3).

The patient was operated on through a left thoracotomy. In addition to a ductus measuring 12 mm. in diameter, there was a mild coarctation of the aorta at the level of the ductus. After division of the ductus, pressures were measured in the aorta proximally and distally to the coarctation the values being 95/68 and 90/75 respectively. Since there was no gradient and no evidence of collateral circulation, it was decided that the minimally coarcted segment should not be excised. The ductus was divided after hypotension had been induced with intravenous Arfonad, the systemic systolic pressure having been lowered from 130 to 80 mm. Hg.

The patient had an uneventful recovery. However, the systolic thrill and murmur persisted unchanged over the suprasternal notch and the aortic area. She was considered to have a residual mild coarctation of the aorta and a bicuspid aortic valve or a mild aortic stenosis. The patient was discharged 11 days after surgery.

Case 10. This twin 2-year-old girl was born prematurely after 6 months and 23 days of pregnancy. Her birth weight was 1,100 Gm., 400 Gm. less than her twin sister's weight. She developed slowly, had repeated respiratory infections, and suffered two episodes of heart failure and pulmonary edema; the first being when she was 14 months of age, when a heart murmur was discovered and digitalization was instituted. Dyspnea and easy fatigability had also been noted. Her twin sister is apparently normal. This patient was studied at a medical center in Paris, France, in February 1957. At cardiac catheterization the catheter was passed from the pulmonary artery into the descending aorta. Oxygen determinations disclosed a left-to-right shunt at the ventricular level. A moderate degree of pulmonary hypertension was also demonstrated. On the basis of these data a diagnosis of patent ductus arteriosus plus a ventricular septal defect was made. She was referred to the University of Minnesota Hospitals for surgical treatment.

On October 30, 1957, physical examination showed a small and underdeveloped girl. Her weight was 6.5 Kg. and her height was 28½ inches. The heart was enlarged, a systolic thrill was present at the base of the heart, and a grade III continuous murmur was heard best in the pulmonary valve area. The pulmonic second sound was accentuated. The blood pressure was 95/60 in the arm and 95/65 in the leg. The femoral pulses were normal. Roentgenograms and fluoroscopy showed an extremely large heart with distinct right ventricular enlargement and slight left atrial enlargement. Both the aorta and the pulmonary artery

FIG. 3. Lateral projection, case 9. Large ductus arteriosus and mild coarctation of aorta clearly visualized.

appeared dilated and the pulmonary vascularity was considerably increased. The electrocardiograms revealed right atrial enlargement and right ventricular hypertrophy. The diagnoses under consideration were a patent ductus plus pulmonary regurgitation and a patent ductus plus ventricular septal defect, which seemed less likely because of the moderate pulmonary hypertension. A retrograde aortogram was undertaken via the right brachial artery with 76 per cent Renographin. The proximal aortic arch and large pulmonary arteries were simultaneously visualized and a ductus was demonstrated. There was no evidence of pulmonary valve insufficiency.

The patient was operated upon through a left thoracotomy incision. A large ductus arteriosus measuring 10 to 12 mm. in diameter was encountered and transected. The patient had an uncomplicated postoperative course. The murmurs totally disappeared and she was dismissed from the hospital 16 days after the operation.

At operation the main pulmonary artery of this infant was found to be greatly enlarged. This patient illustrates the fact that pulmonary regurgitation associated with a patent ductus arteriosus may occur even in the absence of a severe pulmonary hypertension, which characterized the other cases of this series.

Discussion

We have summarized the history and significant physical findings in 10 patients with a left-to-right shunt due to a patent ductus arteriosus, seen at our institution in a 24-month period, all of whom were referred to us for surgical correction of presumed intracardiac lesions. However, each of these patients had a patent ductus arteriosus as the sole malformation responsible for the shunt, and all survived corrective surgery. In 4 patients extracorporeal circulation had been prepared with a consequent loss of valuable operating time. In the first patient of this series, the right ventricle was actually opened before the ductus lesion was recognized.

Subsequent to these chastening experiences in the first 3 patients, our diagnostic acumen has improved to the extent that accurate preoperative diagnosis has been possible in the others, save for the unusual circumstances of case 6.

The fact that 6 of these patients were from widely separated geographic areas indicates that this differentiation has troubled others as well. In fact, conversations with other cardiac surgeons have indicated quite similar experiences.

Thus, it may be worth while to summarize the various signs that have been valuable to us in achieving a correct differential diagnosis between a septal defect and this atypical form of patent ductus arteriosus, with regurgitation of oxygenated blood from the pulmonary artery back into the right ventricle, thus simulating an intracardiac shunt.

History

Gregg,[5] Gibson and Lewis,[6] and others, have emphasized the definite association often existing between the incidence of maternal rubella during pregnancy and a patent ductus arteriosus. In the presence of a doubtful diagnosis and a patient with such a history (as case 3), cardiac catheterization and retrograde aortography should be performed.

Physical Examination

The murmurs and thrills have not been particularly helpful in the differential diagnosis because of the effects of pulmonary hypertension in lessening the diastolic component of the classic continuous murmur of patent ductus arteriosus.[9–11] Moreover, the occurrence of pulmonary diastolic murmur (Graham Steell) in some cases of ventricular septal defect plus pulmonary hypertension[12–14] further confuses the picture. However, bounding peripheral pulses and increased pulse pressure should immediately raise suspicion of a patent ductus arteriosus[15] even though these findings are obviously also indicative of such other possibilities as ventricular septal defect plus aortic insufficiency,[16] ruptured aneurism of the sinus of Valsalva into the right ventricle,[17] arteriovenous fistula of a coronary artery,[18] and aortic septal defect.[19]

Radiologic Findings

As has been well appreciated by many roentgenologists, a left-to-right intracardiac shunt of appreciable magnitude is characteristically associated with a hypoplastic aorta, whereas an extracardiac shunt, such as in patent ductus arteriosus, is accompanied by a large aorta with increased pulsations. This evaluation is facilitated by contrast filling of the esophagus. In infants, in whom a large thymus is frequently present, the interpretation of this sign is usually more difficult.

Electrocardiographic Findings

Usually a small left-to-right shunt through a narrow patent ductus or through a small ventricular septal defect produces no abnormal changes in the electrocardiogram. A wide ductus with a large left-to-right shunt and the consequent overwork for the left ventricle is expressed by the left ventricular hypertrophy. If a significant degree of pulmonary hypertension is superimposed, overburdening of the right ventricle occurs and signs of right ventricular hypertrophy also appear. In ventricular septal defect with increased pulmonary flow and resistance, both left and right ventricular hypertrophy are present. If pulmonary resistance is the salient feature, predominant or isolated right ventricular hypertrophy is generally observed. Thus, the electrocardiogram has offered little

help in the differential diagnosis of these 2 conditions.

Size of the Aorta at Surgery

In the patients of this series were found to have an enlarged aorta at the time of the operation. We believe that whenever this sign is present in a patient undergoing surgery for the correction of a congenital cardiovascular lesion, one should always consider the possibility of a patent ductus arteriosus, either as the sole malformation or combined with an intracardiac shunt. In fact, for some time now in every patient submitted for intracardiac surgery for closure of a ventricular septal defect at our institution the area of the ductus arteriosus is routinely dissected. Fourteen per cent of these patients also had a patent ductus arteriosus and in most cases this condition had not been suspected preoperatively.[20]

In summary, none of these signs is infallible for differentiating a ventricular septal defect from a patent ductus arteriosus. When there is any doubt in the diagnosis, a retrograde aortogram will usually clarify the question.

If there is evidence of a significant shunt through a patent ductus arteriosus and a possible intracardiac septal defect as well, we prefer to manage these lesions at separate operative procedures for the following reasons: 1. If both lesions are actually present, the preliminary division of the ductus with the consequent reduction in pulmonary hypertension will improve the surgical risk for the later closure of the ventricular septal defect. 2. In an appreciable number of patients, as this series indicates, no intracardiac lesions may be found. Such practice also allows maximum use of the pump-oxygenator by avoiding setting it up for cases in which it is not needed.

Surgical Considerations

Patients with patent ductus arteriosus in whom the manifestations are atypical are characterized, as a group, by larger-than-average channels, a condition which together with the significant pulmonary hypertension usually present, nearly always causes a short, thin-walled, tense ductus. Attempts to ligate such a vessel are dangerous and contraindicated in our opinion. The only treatment to be recommended is division between suitable vascular clamps with suture of the divided ends. This procedure is rendered easier and safer by the temporary reduction of systemic and pulmonary blood pressure by use of a vessel relaxant, such as Arfonad,* just prior to application of the clamps, and maintained until suturing has been completed. With the systemic blood pressure reduced to a range of 50-75 mm. Hg the great vessels and ductus become soft, slack, and easily manipulated. Physiologically there is virtually no likelihood of complications from such a temporary period of controlled hypotension.

Table 5.—*Summary*

	Patent ductus arteriosus	Ventricular septal defect
History of rubella 1st trimester of pregnancy	Significant if present	
Peripheral pulses	Bounding	Soft
Blood pressure	Increased pulse pressure	Decreased pulse pressure
Size of aorta	Enlarged	Hypoplastic
Retrograde aortogram	Usually positive	Negative

Summary

Ten patients have been described in whom a patent ductus arteriosus with atypical manifestations closely simulated an intracardiac shunt. All 10 patients had a patent ductus arteriosus as their sole lesion, as demonstrated by successful corrective surgery. The diagnostic criteria of value in leading to a correct differential diagnosis in such patients are reviewed and summarized in table 5. The value of utilizing controlled hypotension at the time of surgical division of patent ducti associated with significant pulmonary hypertension is emphasized.

*Roche Laboratories, Nutley, N. J.

SUMMARIO IN INTERLINGUA

Es describite dece patientes in qui un patente ducto arteriose con manifestationes atypic simulava fortemente un derivation intracardiac. In omne le dece patientes, le chirurgia correctivo—effectuate a bon successo—demonstrava que un patente ducto arteriose esseva le sol lesion. Le criterios diagnostic que es de valor in establir un correcte diagnoses differential in tal patientes es passate in revista e summarisate in tabula 5. Es sublineate le valor del uso de hypotension regulate durante le division chirurgic de patente ductos que es associate con grados significative de hypertension pulmonar.

REFERENCES

1. WARDEN, H. E., COHEN, M., READ, R. C., AND LILLEHEI, C. W.: Controlled cross circulation for open intracardiac surgery. J. Thoracic Surg. **28**: 331, 1954.
2. LILLEHEI, C. W.: Controlled cross circulation for direct vision intracardiac surgery: Correction of ventricular septal defects, atrioventricularis communis, and tetralogy of Fallot. Postgrad. Med. **17**: 388, 1955.
3. —, COHEN, M., WARDEN, H. E., ZIEGLER, N. R., AND VARCO, R. L.: The results of direct vision closure of ventricular septal defects in eight patients by means of controlled cross circulation. Surg. Gynec. & Obst. **101**: 446, 1955.
4. —, —, —, AND VARCO, R. L.: The direct vision intracardiac correction of congenital anomalies by controlled cross circulation. Results of thirty-two patients with ventricular septal defects, tetralogy of Fallot, and atrioventricularis communis defects. Surgery **38**: 11, 1955.
5. GREGG, N. M.: Congenital cataract following German measles in the mother. Tr. Ophth. Soc. Australia **3**: 35, 1941.
6. GIBSON, S., AND LEWIS, K.: Congenital heart disease following maternal rubella during pregnancy. Am. J. Dis. Child. **83**: 117, 1952.
7. RUTSTEIN, D., NICKERSON, R. J., AND HEALD, F. P.: Seasonal incidence of patent ductus arteriosus and maternal rubella. Am. J. Dis. Child. **84**: 199, 1952.
8. ANDERSON, R. C.: Causative factors underlying congenital heart malformations. I. Patent ductus arteriosus. Pediatrics **14**: 143, 1954.
9. CHAVEZ, I., CABRERA, E., AND LIMON, R. La persistencia del conducto arterial complicada de hipertension pulmonar. Arch. Inst. Cardiol. México **23**: 131, 1953.
10. DAMMANN, J. F., JR., GORDON, R. C., SMALL, M. A., AND CHIR, M. B. B.: Patent ductus arteriosus in the absence of a continuous murmur. Circulation **6**: 111, 1952.
11. ADAMS, P., JR., ADAMS, F. H., VARCO, R. L., DAMMANN, J. F., AND MUELLER, W. L.: Diagnosis and treatment of patent ductus arteriosus in infancy. Pediatrics **12**: 64, 1953.
12. KJELLBERG, S. R., MANNHEIMER, E., RUDHE, V., AND JONSSON, B.: Diagnosis of Congenital Heart Disease. Chicago, Year Book Publishers, Inc., 1955, p. 262.
13. NADAS, A. S.: Pediatric Cardiology. Philadelphia and London, W. B. Saunders Company, 1957, p. 315.
14. SILVER, A. W., KIRKLIN, J. W., ELLIS, F. H., JR., AND WOOD, E. H.: Regression of pulmonary hypertension after closure of patent ductus arteriosus. Proc. Staff Meet. Mayo Clin. **29**: 293, 1954.
15. GASUL, B. M., FELL, E. H., DILLON, R., AND MARIENFELD, L. H.: Diagnosis and treatment of the malignant type of patent ductus arteriosus in infants: Clinical, angiocardiographic and cardiophysiologic study of 12 patients. Transactions of the Annual Meeting of the American Heart Association. Chicago, 1954.
16. WINCHELL, P., AND BASHOUR, F.: Ventricular septal defect with aortic incompetence simulating patent ductus arteriosus. Am. J. Med. **20**: 361, 1956.
17. LILLEHEI, C. W., STANLEY, P., AND VARCO, R. L.: Surgical treatment of ruptured aneurysms of the sinus of Valsalva. Ann. Surg. **146**: 459, 1957.
18. DAVIS, C., JR., DILLON, R. F., FELL, E. H., AND GASUL, B. M.: Anomalous coronary artery simulating patent ductus arteriosus. J.A.M.A. **160**: 1047, 1956.
19. GIBSON, S., POTTS, W. J., AND LANGEWISH, W. H.: Aortic pulmonary communication due to a localized congenital defect of the aortic septum. Pediatrics **6**: 357, 1950.
20. LILLEHEI, C. W., WARDEN, H. E., DEWALL, R. A., STANLEY, P., AND VARCO, R. L.: Cardiopulmonary bypass in surgical treatment of congenital or acquired cardiac disease. A.M.A. Arch. Surg. **75**: 928, 1957.

Excessive Urinary 5-Hydroxy-3-Indole Acetic Acid in the Absence of a Metastatic Carcinoid

By FABER F. MCMULLEN, JR., M.D., AND HUGH H. HANSON, M.D., F.A.C.P.

Considerable interest has been aroused in the diagnosis of the malignant carcinoid syndrome and the diagnostic reliability of increased urinary excretion of 5-hydroxy-3-indole acetic acid. The authors present observations important to this problem.

THE colorimetric test allegedly specific for the malignant carcinoid syndrome was recently observed to be strongly positive in 2 patients who did not have this disease.

Observation of excessive elevation of urinary 5-hydroxy-3-indole acetic (5-HIAA) by the qualitative chemical test of Udenfriend and co-workers has been considered a specific, simple, rapid, and reliable means of recognizing the presence of metastatic carcinoid tumors.[1-3] This test of the urine of 1,023 patients selected at random by one investigator revealed uniformly negative results and prompted the conclusion that a false positive test due to drugs or other clinical conditions, if present at all, must be very rare.[4] Recently 2 patients were observed who had symptoms prompting suspicion of the malignant carcinoid syndrome. The urine of both patients revealed well elevated levels of 5-HIAA by both the colorimetric test of Udenfriend and co-workers[2-5] and the paper chromatographic test of Curzon.[6] Subsequent investigations failed to demonstrate a carcinoid tumor in either patient. The exact specificity of this generally accepted colorimetric test for 5-HIAA is not known, and the reliability of the test in making a diagnosis of the malignant carcinoid syndrome is questioned.

The clinical features of the malignant carcinoid syndrome may be divided into the following groups: (1) cutaneous vascular lesions (paroxysmal or permanent erythematous flushing of the skin, intermittent patchy cyanosis and blanching), (2) gastrointestinal features (abdominal pain, diarrhea, hepatomegaly, and ascites), (3) cardiovascular manifestations (progressive exertional dyspnea, syncope, asthma, hypotensive states, right heart failure, and tricuspid and pulmonary valvular lesions), and (4) metabolic derangements (increased levels of serotonin in the blood, extreme elevations of 5-HIAA in the urine, peculiar personality changes, and definite psychotic episodes).

The excessive production of 5-hydroxytryptamine (serotonin, enteramine, 5-HT) from its dietary precursor tryptophan by the tumor tissue is allegedly the initiating step of the symptom complex.[7-8] Tumors yielding as high as 2.5 mg. of 5-HT per Gm. of tissue have been reported.[9] Subsequent metabolism of 5-HT results in the formation of 5-HIAA, which is excreted in the urine. The major chemical alterations in the malignant carcinoid syndrome therefore consist of elevated blood levels of 5-HT[10] and greatly elevated levels of urinary 5-HIAA.[11]

The normal 5-HT in the serum ranges from 0.03 to 0.2 μg. per ml.[12] and in the urine from 0.01 to 0.7 μg. per ml.[13] The normal 24 hour urinary excretion of 5-HIAA ranges between 2.0 and 10.0 mg.[2, 4, 5] In the malignant carcinoid syndrome the serum level of 5-HT has been found to range from 0.2 to 6.5 μg. per ml.[12-14] and the urinary 5-HIAA from 60 to 2,000 mg. per 24 hours.[8-15]

CASE REPORTS

Case 1. A 28 year old white salesman was admitted to Hermann Hospital January 4, 1958, with a long history of emotional disturbances, a 10 year history of diabetes mellitus, and a recent onset of intermittent dizziness, numbness of the left face, arm, and hand, weakness, nausea with emesis,

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ataxic gait, and a sensation of "blacking out." He also experienced postprandial nervousness, accompanied by flushing of the face and neck. Three months prior to admission, he had been found hypertensive and given rauwolfia serpentina (Raudixin) 100 mg. twice daily with a subsequent exaggeration of symptoms. This medication had been discontinued after 2 weeks and had not been taken for the 2 months preceding hospitalization.

Physical examination revealed the patient to be 68 inches in height, to weigh 201 pounds, to have a blood pressure of 150/110, and a pulse of 84 per minute. The heart was slightly enlarged without murmurs or thrills. The lungs were clear. The liver was not palpably enlarged. The genitalia were normal, and proctoscopic examination was not remarkable.

Laboratory studies revealed the patient to have a normal hemogram, serum cholesterol 504 mg. per cent, protein-bound iodine 5.4 μg. per cent, blood urea nitrogen 9.9 mg. per cent, phenolsulfonphthalein excretion 20 per cent in 15 minutes and 63 per cent in 2 hours, and a diabetic 3 hour glucose tolerance curve. The liver function tests included a cephalin-cholesterol flocculation 1 plus at 48 hours, thymol turbidity 2.6 units, alkaline phosphatase 3.5 Bodansky units, serum glutamic oxaloacetic transaminase 23 units, serum glutamic pyruvic transaminase 32 units, bromsulphalein retention 0 at 45 minutes, albumin 4.3 Gm. per cent, and globulin 2.7 Gm. per cent. The 24-hour urine specimen contained 1.5 μg. epinephrine, 31 μg. norepinephrine, 2.4 mg. 17-hydroxycorticosteroids, and 17.4 mg. 17-ketosteroids. The electroencephalogram revealed a poorly organized and regulated, moderately slow electrogram showing no focal or lateralizing signs. These findings were consistent with a moderate alteration of cerebral function of nonspecific etiology. Roentgenograms of the skull, chest, and upper gastrointestinal tract, small bowel, colon, and vertebral column were normal. The urinary 5-HIAA was reported strongly positive. On the basis of the latter test the patient was subjected to surgical exploration for a suspected malignant carcinoid tumor. At surgery, the contents of the abdomen were without note except for a slight asymmetry of the adrenal glands. The patient subsequently had a bronchoscopic examination that was also normal.

Case 2. A 68 year old white male executive was admitted to Hermann Hospital January 3, 1958, because of weakness, nausea, and pain in the right upper quadrant of the abdomen and the right costovertebral angle. He had experienced a perforated duodenal ulcer in 1912, massive upper gastrointestinal hemorrhages in 1943 and 1951, and subtotal gastrectomy in 1956. Postoperatively, there was dehiscence of the duodenal stump with resultant shock; however he recovered under conservative management. Subsequently the patient developed a right upper quadrant pancreatic fistula that opened and closed 3 times prior to the last hospitalization.

Physical examination revealed the patient to be 74 inches tall and to weigh 180 pounds. The blood pressure was 120/80 and the pulse 84 per minute and regular. The patient appeared acutely ill. A draining right upper quadrant fistula was present. The liver was enlarged and palpable 3 to 4 cm. below the right costal margin. Tenderness on percussion was marked in the right upper quadrant. The remainder of the examination was not remarkable.

Laboratory examinations revealed a normal hemogram, corrected erythrocyte sedimentation rate 34 mm. in 1 hour, serum amylase 17 to 30 mg. per cent, serum lipase 1.5 mg. per cent, blood urea nitrogen 21 to 34 mg. per cent, and creatinine 2.6 mg. per cent. The liver function tests revealed cephalin-cholesterol flocculation 1 to 4 plus, thymol turbidity 0.9 to 2.0 units, alkaline phosphatase 10 to 24 Bodansky units, serum bilirubin 0.6 mg. per cent, serum glutamic oxaloacetic transaminase 32 units, prothrombin time 13 seconds with a 12 second control, and bromsulphalein retention of 5.0 per cent at 45 minutes. Roentgenograms of the chest, upper gastrointestinal tract, colon, and vertebral column were within normal limits.

Under observation the liver continued to enlarge, became very nodular, and the patient developed a peculiar type of erythematous flushing of the head and neck associated with paroxysmal episodes of respiratory distress prompting the determination of the urinary 5-HIAA. The laboratory examination by both of the previously mentioned methods was strongly positive for 5-HIAA. The patient deteriorated rapidly and died on March 3, 1958. Postmortem examination revealed a carcinoma of the body and head of the pancreas with metastasis to the liver. No evidence of a carcinoid tumor was found.

Discussion

In this communication the cases of 2 patients manifesting signs and symptoms prompting consideration of the malignant carcinoid syndrome in the differential diagnosis are reported. Both revealed high levels of urinary 5-HIAA determined by the 2 previously mentioned methods.[2, 5, 6] Although extensive studies in these patients included bronchoscopic examination and exploratory laparotomy in one and postmortem examination in the other, in neither was a carcinoid tumor found. The colorimetric test for the

detection of 5-HIAA is based on the appearance of a purple color on addition of 1-nitroso-2 naphthol, nitrous acid, and ethylene dichloride to the urine; the intensity of the color is directly proportional to the concentration of the 5-HIAA. Unfortunately, this test is not specific for 5-HIAA but is specific for 5-hydroxyindoles;[2-5] therefore, a positive test may be obtained in the presence of all the intermediary compounds of tryptophan metabolism having the 5-hydroxyindole configuration. Urine containing acetyl p-aminophenol, the end-metabolic product of p-hydroxyacetanilid, gives a positive test, as does the urine after excessive consumption of bananas.[3-4] Under these circumstances, a false positive test for the malignant carcinoid syndrome may occur. Neither patient here considered received acetanilid or consumed bananas prior to their urinary tests for 5-HIAA. It is worthy of consideration that 5-hydroxyindoles may exist in elevated amounts in pathologic and physiologic states other than the malignant carcinoid syndrome.

Three cases of the malignant carcinoid syndrome have been reported in which 5-hydroxytryptophan was secreted by the tumor and excreted as such in the urine.[16]

The only logical explanation for these 2 false positive tests in the absence of a malignant carcinoid must be that 5-hydroxyindoles other than 5-HIAA were present in the urine and resulted in a false positive test for 5-HIAA, or that elevated urinary 5-HIAA is common to conditions other than the malignant carcinoid syndrome. This report is given in the thought that it may prevent unnecessary surgery on the basis of this test, and in the hope of stimulating further investigation regarding the urinary excretion of 5-HIAA.

Summary

The cases have been presented of 2 patients, with strongly positive tests for urinary 5-HIAA, in which a malignant carcinoid tumor did not exist. From the observations made here, it would appear that the accepted test for urinary 5-HIAA may not be specific for the compound alone, and the presence of other 5-hydroxyindoles may result in a false positive test. It is also possible that high urinary concentration of 5-HIAA exists in pathologic and physiologic states other than the malignant carcinoid syndrome. The specificity of the commonly used test for urinary 5-HIAA in the malignant carcinoid syndrome needs further investigation.

Summario in Interlingua

Es presentate le casos de 2 patientes con fortemente positive tests urinari pro acido 5-hydroxy-3-indole-acetic in le absentia de omne maligne tumor carcinoide. Super le base del observationes hic reportate, il pare que le currentemente acceptate test pro le presentia de acido 5-hydroxy-3-indole-acetic in le urina non es specific pro ille composito sol e que le presentia de altere 5-hydroxy-indoles pote resultar in false positivitate. Il es etiam possibile que alte concentrationes urinari de 5-hydroxy-3-indole-acetic existe in statos pathologic e physiologic altere que illo del syndrome de maligne tumor carcinoide. Le specificitate del communmente usate test pro acido 5-hydroxy-3-indole-acetic in le urina in casos del syndrome de maligne tumor carcinoide require investigationes additional.

REFERENCES

1. Mattingly, T. W., and Sjoerdsma, A.: The cardiovascular manifestations of functioning carcinoid tumors. Mod. Concepts Cardiovas. Dis. **25**: 337, 1956.
2. Sjoerdsma, A., Weissbach, H., and Udenfriend, S.: Simple test for diagnosis of metastatic carcinoid (argentaffinoma). J.A.M.A. **159**: 397, 1955.
3. Waalker, T., Sjoerdsma, A., Creveling, C., Weissbach, H., and Udenfriend, S.: Serotonin, norepinephrine, and related compounds in bananas. Science **127**: 648, 1958.
4. Mohler, D.: Evaluation of the urine test for serotonin metabolites. J.A.M.A. **163**: 1138, 1957.
5. Udenfriend, S., Titus, E., and Weissbach, H.: The identification of 5-hydroxy-3-indole-acetic acid in normal urine and a method of its assay. J. Biol. Chem. **216**: 499, 1955.
6. Ross, G., Weinstein, B., Kabakow, B.: The influence of Phenothiazine and some of its derivatives on the determination of 5-hydroxyindoleacetic acid in the urine. Clin. Chem. **4**: 66, 1958.

7. THORSON, A., BJORCH, G., BJORKMAN, G., AND WALDENSTROM, J.: Malignant carcinoid of the small intestine with metastases to the liver, valvular disease of the right side of the heart, peripheral vasomotor symptoms, bronchoconstriction, and an unusual type of cyanosis. A clinical and pathologic syndrome. Am. Heart J. **47**: 795, 1954.
8. UDENFRIEND, S., WEISSBACH, H., AND BODANSKI, D.: Increase in tissue serotonin following administration of its precursor, 5-hydroxytryptophan. J. Biol. Chem. **224**: 803, 1957.
9. LEMBECK, F.: 5-Hydroxytryptamine in a carcinoid tumor. Nature **172**: 910, 1953.
10. PERNOW, B., AND WALDENSTROM, J.: Paroxysmal flushing and other symptoms caused by 5-hydroxytryptamine and histamine in patients with malignant tumors. Lancet **267**: 951, 1954.
11. HANSON, A., AND SERIN, F.: Determination of 5-hydroxyindoleacetic acid. Lancet **269**: 1359, 1955.
12. SHARMAN, D. F., AND SULLIVAN, F. M.: 5-Hydroxytryptamine in the serum. Nature **177**: 332, 1956.
13. TWAROG, B. M., AND PAGE, I. H.: Serotonin content of some mammalian tissues and urine. Am. J. Physiol. **175**: 157, 1953.
14. SNOW, P. J. D., LENNARD, J. E., CURZON, G., AND STACEY, R. S.: Humeral effects of metastasizing carcinoid tumors. Lancet **269**: 1004, 1955.
15. PERNOW, BENGT, WALDENSTRON, JAN.: Determination of 5-hydroxytryptamine, 5-hydroxyindoleacetic acid and histamine in thirty-three cases of carcinoid tumor. Proc. Internatl. Physiol. Congress, 1956, p. 715.
16. SANDLER, M., AND SNOW, P. J. D.: An atypical carcinoid tumor secreting 5-hydroxytryptophan. Lancet **1**: 137, 1958.

Medical Eponyms

By ROBERT W. BUCK, M.D.

von Graefe's Sign. This was described by Albrecht v. Graefe (1828-1870) at a meeting of the Berlin Medical Society on March 9, 1864, and was reported in the *Deutsche Klinik* 16: 158 (April 16) 1864, under the title "Basedow's Disease" (*Ueber Basedow'sche Krankheit . . . .*)

"When we cause the healthy person to look up and down, the upper eyelid moves correspondingly. In those suffering with Basedow's disease, this motion is almost completely abolished or reduced to a minimum; that is, when the cornea is turned downward, the upper eyelid does not follow. This is not a direct result of the exophthalmos, because in the presence of tumors of the orbit or other causes of protrusion, the symptom is frequently absent, although in very marked degrees the motions of the lid are naturally interfered with. On the other hand, it is present in the mildest degrees of exophthalmos in Basedow's disease . . . It is apparently to be regarded as a peculiar disturbance of the innervation of the muscles of the eyelid."

Functional Diagnosis of Patent Ductus Arteriosus Studied by Cineangiocardiography in Fifty-three Cases

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With the technical assistance of Virian A. Palladoro, B.S.

The hemodynamic alterations revealed by cineangiocardiography in 53 cases of patent ductus arteriosus made possible the correct angiocardiographic diagnosis in 90 per cent of the cases. The most constant functional sign is "blanching of the pulmonary artery," which is seen during diastole and consists of a decrease in density of the pulmonary artery and its branches. This phenomenon has been analyzed by projecting the cineangiocardiograms frame by frame and measuring angiographic density and diameter at the same points of the pulmonary artery. The curves obtained were correlated with each other and plotted against time. The findings were correlated with clinical, surgical, and pathologic information. The hemodynamics of the shunt in patent ductus arteriosus are discussed and a theoretical explanation is offered.

PATENT ductus arteriosus is one of the most frequent congenital cardiac anomalies. This condition occurred in 24.2 per cent of the cases in the Abbott report on 1,000 autopsies of congenital heart diseases,[1] and Heim de Balsac[2] found this same incidence. The ductus was patent in 18 per cent of the congenital heart cases studied in our department. According to Benn[3] and Lynxwiler and Wells,[4] this anomaly occurs more frequently in females (66 per cent), whereas in our statistics the distribution is the same for both sexes. Patent ductus arteriosus was complicated by other congenital anomalies in 66 per cent of Abbott's cases, in 61 per cent of Castellanos,[2] and in 36 per cent of our cases.

The "isolated" form of patent ductus arteriosus does not present diagnostic difficulties. However, the clinical diagnosis of the "complicated" forms may offer a problem, especially when catheterization, gas analysis, and other procedures are inconclusive.[2, 5-8]

Because of the evolution of the disease itself, the anatomic alterations may be quite variable[9] and in many cases the heart has a normal configuration. Departures from the norm, that are sometimes referred to as "typical," are actually not specific and are common to other anomalies. Conventional angiocardiography has been reported to be unreliable in the diagnosis of patent ductus arteriosus.[10-14] Because of the low exposure frequencies (2 to 4 films per second) this technic has failed to represent all phases of the cardiac cycle[15] and thus the altered hemodynamics, which are the reliable indicators of the underlying changes, often were undetected.

It is our opinion that the diagnosis of patency of the ductus arteriosus can be based on functional alterations due to the aortic-pulmonary artery shunt. These phenomena can be demonstrated by high-speed angiocardiography giving at least 6 exposures *per cardiac cycle*, and can be studied in some detail when the exposure frequency reaches a minimum of *10 per cardiac cycle*. The cineangiocardiographic method, with its high exposure fre-

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TABLE 1.—*Changes in Optical Transmission in the Pulmonary Artery of Normal Hearts and Cases with Patent Ductus Arteriosus*

Cardiac cycle	1	2	3	4	5	6
Trunk						
Normal	9.25*	5.25	3.50	2.75	0.00	0.00
Ductus	14.92	10.00	10.80	9.08	6.80	4.24
Bifurcation						
Normal	16.50	9.00	5.00	4.00	0.00	0.00
Ductus	17.00	20.00	18.75	16.41	11.00	7.37
Left branch						
Normal	15.00	8.50	7.50	4.50	3.50	0.00
Ductus	15.70	16.00	14.43	13.43	7.31	7.25

*The averages of the differences between the maximum diastolic, optical transmission and the minimum systolic optical transmission measured in 6 consecutive cardiac cycles of the right cineangiocardiogram of the trunk, on the bifurcation and on the left branch of the pulmonary artery in 15 normal hearts and in 30 cases of patent ductus arteriosus. This table shows that in patent ductus arteriosus the angiographic density of the pulmonary artery decreases far more than in normal cases, especially after the second cardiac cycle. This phenomenon is caused by the dilution of contrast material in the pulmonary artery by the blood coming from the aorta via the ductus.

Optical density can be measured as "absorption" or as "transmission." Transmission expresses the quantity of light emerging from the film and projected on the screen. The quantity of emerging light measured on the pulmonary artery before the passage of the contrast material was made equal to 100 per cent transmission. The measurement obtained in this manner expresses the ratio between the actual density and the density measured before the passage of contrast material. These measurements are comparable to each other in the same film and to those in other films because they are not affected by the variation of density (due to the factor of exposure, the processing, and the printing and finally the technic of projection).

quencies (15, 30, or 60 frames per second), permits the study of the hemodynamics of both "isolated" and "complicated" patent ductus arteriosus.

This paper describes the cineangiographic findings and discusses possible correlation with the physiopathology of the aortic-pulmonary artery shunt and the differential diagnosis.

MATERIALS AND METHODS

Fifty-three cases of patent ductus arteriosus, representing 18 per cent of the congenital heart cases observed in our department, have been studied by cineangiocardiography.

The clinical study of each patient included physical examination, electrocardiogram, and phonocardiogram. Successful cardiac catheterization studies were obtained in 16 patients, surgical findings were available in 30, and autopsy findings in 3.

Cineangiocardiography was performed on unanesthetized patients seated in an oblique position, usually left anterior oblique or right posterior oblique. The cineangiocardiograms were recorded on either 35- or 70-mm. film at camera speeds of 15, 30, or 60 frames per second.[16, 17] A special analytic projector developed in this department[18] was used to view the 16-mm. reduction prints.

The contrast media used were 70 per cent Diodrast and 70 per cent Urokon. The dose injected was 1 to 1.5 ml./Kg. of body weight. The contrast medium was injected by an ordinary syringe or semiautomatic injector, into the veins of the arm through a polyethylene tube or into the superior vena cava through a Cournand or a Lehman catheter.

The movements of the heart structures and great vessels have been represented graphically by the new method of cineardiometry.[19] The borders of the heart chambers and great vessels were traced from single frame projections[18] of the cineangiocardiographic films. By utilizing specific anatomic reference points, diameters and area were measured on the drawings and their percentage deviations from their arithmetic average were plotted against time. Specific curves were obtained from these measurements showing the variations of chosen diameters and areas. These curves are similar to electrokymographic tracings and can be correlated with angiographic density curves recorded at the same time. These density changes of the chosen areas of the heart

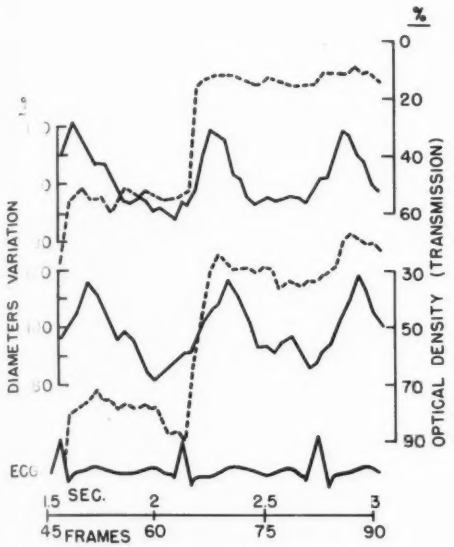

FIG. 1. Angiographic density (*dotted lines*) and vessel diameter (*solid lines*) measured on trunk (*upper curves*) and on the left branch (*lower curves*) of pulmonary artery of normal cineangiocardiogram in left anterior oblique position at 30 frames/sec. Electrocardiographic tracing at *bottom* of figure recorded synchronously. The angiographic density of the pulmonary artery reaches a plateau with the second cardiac cycle of the right angiocardiogram. Slight variations of density due to change in diameter of vessel (pulsation).

and great vessels have been recorded by projecting the films, frame by frame, on a specially adapted screen and measuring the optical density with a densitometer.

RESULTS

The *angiographic density* of the pulmonary artery has been measured in the first 6 consecutive cardiac cycles of right cineangiocardiograms in normal subjects and in those with patent ductus arteriosus.

In the normal subject, the angiographic density of the pulmonary artery usually reaches the maximum during the second cardiac cycle of the right angiocardiogram following peripheral injection of medium. See figure 1. The degree of opacification of the vessel depends upon concentration, quantity, and flow rate of the contrast medium injected and upon the heart rate. Other factors being equal, the greater the heart rate, the less is the concentration of contrast medium per stroke volume.

The angiographic density of the pulmonary artery is greater in the trunk than in the branches. This density is proportional to the cross-sectional area of the vessels except for density changes produced by overlapping structures.

In normal subjects, the angiographic density of the vessels decreases during diastole and may be seen by gross inspection during the first 2 cardiac cycles of the right angiocardiogram. This is due to the mixing of the contrast medium with the blood present in the vessel during the first and second cycles. In the other cycles, if the injection, which is too slow, is discounted, the density depends on the systolic-diastolic variation of the cross-sectonal area of the vessel (pulsation).

Differences between systolic and diastolic angiographic density have been measured at 3 different points on the pulmonary artery (trunk, bifurcation, and left branch) in each of the first 6 consecutive cardiac cycles of the right angiocardiogram. In table 1 are reported the averages of these differences measured in 15 normal cases and in 30 cases with patent ductus arteriosus. The density is expressed as optical *transmission* (table 1, foot note). Thus, 9.25 (table 1, cycle 1, trunk, normal) means that the *transmission* of the light of the projector at the same point on the trunk of the pulmonary artery is 9.25 per cent greater in diastole than in systole, i.e. the *opacity* of the vessel at that point is diminished. The data of table 1 demonstrate clearly that a diastolic loss of density occurs during the first 2 cardiac cycles of the right angiocardiogram in both normal and patent ductus arteriosus cases; and that in subsequent cardiac cycles, diastolic loss of density in patent ductus arteriosus is 2 or 3 times more than in normal subjects, particularly at the bifurcation of the pulmonary artery (fig. 2).

According to our experience, this diastolic loss of density in the pulmonary artery is visible by gross observation during the projection of the films when the diastolic *trans-*

TABLE 2.—*Timing of Blanching Sign*

Duration of cardiac cycle (sec.)	No. cases	"Blanching time" at bifurcation of pulmonary artery average beginning* (%)	Average age of patients in each group
0.80	2	41	29 (27-31)
0.73	4	27	4.6 (3-6)
0.67	4	40	10.8 (3-28)
0.57	1	46	10
0.535	2	43.5	6.5 (6-7)
0.50	1	30	5
0.466	3	37	6.6 (5-11)
0.40	3	58	6.3 (5-9)
0.60	20	39.9	

*Elapsed time between onset of ventricular ejection and beginning of blanching sign expressed as percentage of duration of cardiac cycle.

mission increases above 5 or 6 per cent. For this reason (table 1) the phenomenon, "blanching sign of the pulmonary artery," is always visible in cases of patent ductus arteriosus.

We attempted to determine the onset of the "blanching" in 20 cases by plotting against time the variation of angiographic density and pulsation of the pulmonary artery (table 2). The beginning of the blanching was measured from the start of the ventricular ejection, which is always recognizable on the films projected in single frame and on the density tracings. The time in each case was expressed as a percentage of the duration of the cardiac cycle.

We found (table 2) that the "blanching of the pulmonary artery" began after a lapse of about 39/100 of the cardiac cycle. This is in diastole because, according to the electrokymographic findings of Heyer et al.,[22] diastole begins 20 to 29/100 after the onset of ejection. In only 2 cases presenting a very wide and short ductus was the "blanching" demonstrable at the end of systole.

This cineangiocardiographic sign (blanching of pulmonary artery) was noted by members of this department and described in 1952.[20] It represents the dynamic aspect of the iconographic defect of opacification of the left branch of the pulmonary artery, described by Goetz in 1951[21] as the "jet sign" and by Dotter and Steinberg[12, 14] in the same year as dilution of contrast medium in the left branch of the pulmonary artery.

The "blanching" observed by continuous projection consists of a loss of density of the contrast shadow of the pulmonary artery; it occurs during diastole and is demonstrable in each cardiac cycle of the right angiocardiogram. The blanching starts at the bifurcation of the pulmonary artery or at one of its branches, most often the left. It descends retrogradely toward the pulmonary valves and may involve the distal two thirds of the trunk (fig. 3). At the same time the *blanching* progresses forward into the branches of the pulmonary artery. Occasionally the most evident changes in density were demonstrable in the branches when the trunk was obscured by overlying structures resulting from the positioning of the patient.

The *blanching sign* was demonstrable in *isolated* patent ductus arteriosus and in those complicated by interatrial septal defects, pulmonary valvular stenosis, coarctation of the aorta and in 1 case of ductus with bidirectional shunt.

We could not demonstrate any "blanching sign" in a case of left-to-right shunt due to partial anomalous venous return, atrial and ventricular septal defect and in a case of pulmonary stenosis.

We attempted to correlate the magnitude of the "blanching sign" with that of the shunt measured by catheterization and gas analysis. Table 3 demonstrates no direct relationship. lique projection. For this reason we missed completely the study of one of the branches of the pulmonary artery. We think that the amount of "blanching" measured on the The findings presented have been observed in cineangiocardiograms recorded in only 1 of trunk and both branches of the pulmonary artery, as recorded by biplane cineangiocardiography, should be proportional to the

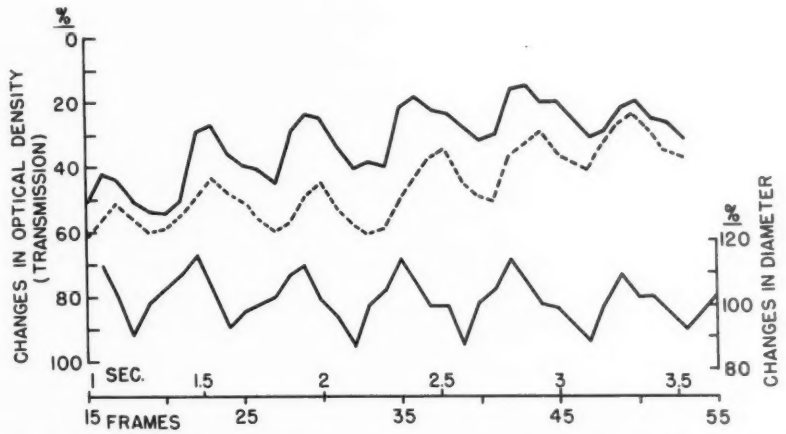

FIG. 2. Angiographic density of pulmonary artery measured on trunk (*solid line, top*) and on left branch (*dotted line*) correlated with diameter changes of trunk (*solid lines, bottom*) from a 15-frames/sec. left anterior oblique cineangiocardiogram in 7-year-old girl with patent ductus arteriosus. Angiographic density of pulmonary artery decreases in diastole 3 times more than in normal case. See figure 1. Density variation of trunk and left branch occurs at same time. Third cardiac cycle corresponds to figure 3.

amount of the shunt measured by gas analysis. However, if we consider the size of the ducti found at surgery and reported in table 3, there is some doubt about the catheterization and gas analysis methods in measuring the amount of blood shunted from the aorta into the pulmonary artery via the ductus.

The *reopacification of the pulmonary artery* occurring during the left angiocardiogram is another well-known angiocardiographic sign of patent ductus arteriosus. It may be difficult to differentiate it from a persistent opacification of an enlarged pulmonary artery and from any other left-to-right shunt.

For technical reasons, we could study this angiocardiographic sign by densitometry and cine-electrokymography in only 5 cases. Densitometric tracings show that the density of the pulmonary artery begins to increase during diastole (reopacification).

This demonstrated that the "blanching sign" and reopacification of the pulmonary artery are a reciprocal aspect of the same phenomenon seen in different phases of the angiocardiogram, namely the diastolic component of the shunt coming from the aorta into the pulmonary artery via the ductus.

DIFFERENTIAL DIAGNOSIS AND DISCUSSION

Are the "blanching sign" and the "reopacification" of the pulmonary artery specific for isolated patent ductus arteriosus? Consider some other congenital communications between the aorta and the pulmonary artery. These have been classified[2, 24] as *low* or juxtaorificial communications and *high* communications at the level of the trunk or branches of the pulmonary artery.

We have not had the opportunity to study any of these anomalies by cineangiocardiography, but we believe that it should be possible, theoretically, to differentiate the *low* communications from isolated patent ductus arteriosus. The anatomic position of such a communication should produce a low defect of opacification of the trunk of the pulmonary artery or of the ascending aorta. The direction or vector of the blanching in this case should be mainly forward, toward the bifurcation and not retrograde as in patent ductus arteriosus, and lastly, the pulmonary artery enlargement, according to the descriptions of the few reported cases,[2] should be greater in the low communications than in ductus.

It could be difficult to differentiate ductus

TABLE 3.—*Correlation of Magnitudes of Blanching Sign and Shunt*

No.	Cine. No.	Age	Sex	Roentgen position	Complications	Pulm. art. pressure	Shunt (% SBF*)	Size ductus at surgery: Length	Size ductus at surgery: Ext. diam.	"Blanching"†: Bifurcation	"Blanching"†: Left branch
1	1080	6	M	LAO	Coaret. Aorta	68-39	93%	large	——	18.33	26
2	1290	6	F	LAO		17-8	59%	long	mm. 3	11	8
3	1060	27	M	LAO		24-8	57%	small	mm. 5	7	
4	1070	10	F	LAO		21-9.5	45%	very small	——	13	10.
5	1176	21	F	LAO		21-10	36%	?	?	11.33	11.
6	1112	5	F	LAO	Coaret. aorta	30-18	36%	short	mm. 5	7.43	5.
7	1172	5	M	LAO		26-14	31%	?	mm. 4	29.33	19.
8	877	6	M	RPO	Pulmonic stenosis	17-7	30%	found during valvulotomy		21.75	16

*SBF = Systemic blood flow

†Averages of diastolic loss of density (transmission) in 6 consecutive cardiac cycles of right cineangiocardiograms on bifurcation and on left branch of the pulmonary artery.

This table shows that the blanching sign measured in cineangiocardiograms recorded in only one oblique projection is not proportional to the amount of the aorta-pulmonary artery shunt measured by catheterization and gas analysis.

from *high* aortic-pulmonary communications. We noted in 2 cases of patent ductus arteriosus of the "window type"[25] that the diastolic blanching was associated with a systolic defect of opacification of the left branch and bifurcation of pulmonary artery. No such systolic defect was detectable in the other types of ductus,[25] the "cylindrical" and "funnel." For this reason we believe that it would be impossible to differentiate between the "window-type" ductus and the *high* aortic-pulmonary communication, which functionally behaves in the same manner. However, the latter condition is extremely rare. Only about 30 cases were described between 1860 and 1949.[2, 24-30]

In our cases of *ductus complicated by other defects*, we observed that the "blanching sign" and reopacification of the pulmonary artery were present in all 7 cases complicated by coaretaton of the aorta. The "blanching" was also present in 7 cases complicated by pulmonary stenosis. In these cases the pulmonary artery was greatly enlarged, especially at the bifurcation, and it pulsated vigorously. The reopacification of the pulmonary artery was confused by the persistence of the contrast material in the enlarged vessel.

In 2 cases complicated by pulmonary stenosis and interatrial septal defects, the findings were identical with the cases complicated by pure pulmonary stenosis. The blanching and reopacification were not demonstrable in 2 of the 3 cases complicated by multiple defects; one of these was in a patient with tricuspid atresia and aortic stenosis and the other in a patient with atrioventricularis communis.

It is our opinion that the blanching sign should be demonstrable in all cases of complicated patent ductus arteriosus when the hemodynamics pertinent to the complicating anomalies allow a sufficiently large shunt of relatively nonopaque aortic blood into a pulmonary artery well filled with contrast medium.

We have observed that in complicating intracardiac shunts the angiographic density of the pulmonary artery does not change during the cardiac cycle, since the blood is mixed upstream from the semilunar valves.

In considering the significance of the diastolic timing of the "blanching" and "reopacification of the pulmonary artery," certain hemodynamic and mechanical factors must be considered. Regardless of the timing

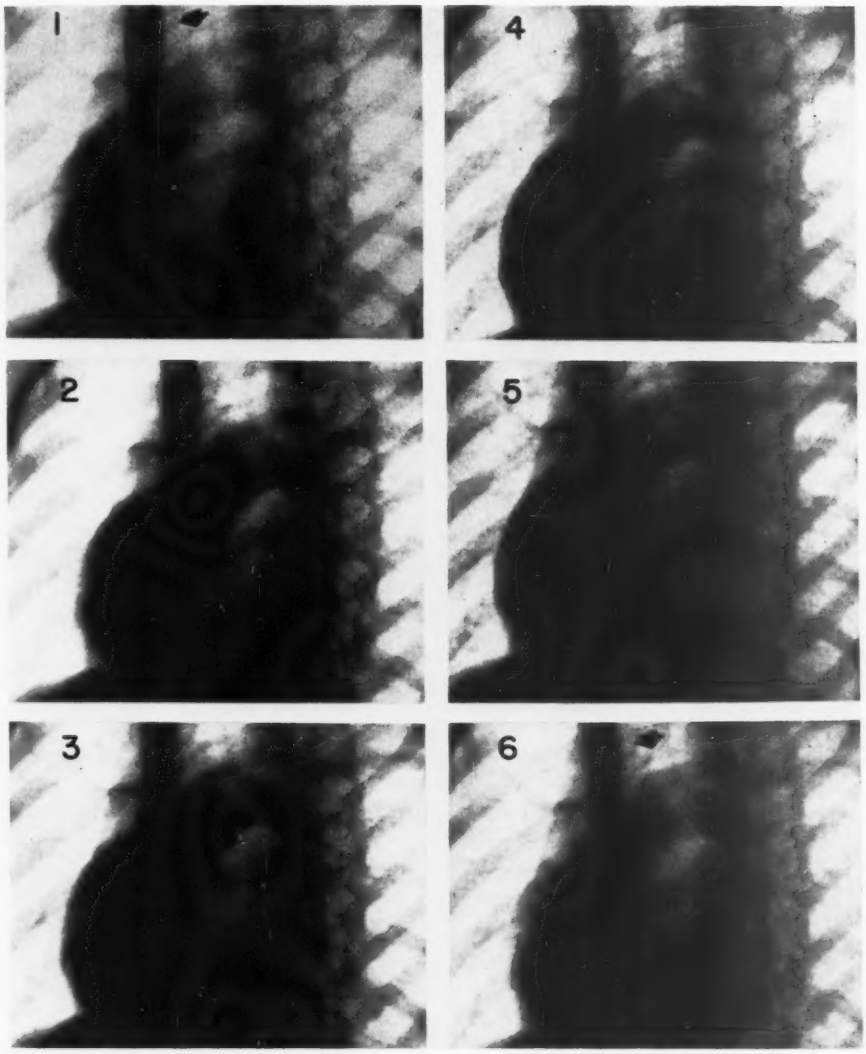

FIG. 3. Sequence from 15-frames/sec. cineangiocardiogram in 7-year-old girl with patent ductus arteriosus. Cardiac cycle recorded by 7 frames (0.47 sec.). At surgery ductus measured 4 mm. outside diameter and 4 mm. in length. Typical machinery murmur and normal ECG found. Angiographic density of trunk and left branch of pulmonary artery less in diastole (*1* and *6*) than in systole (*2* to *5*). See third cardiac cycle in figure 2. This cyclic diastolic density change of pulmonary artery as observed on cineangiocardiogram by continuous projection is "blanching sign of the pulmonary artery." Band of lesser density in distal portion of pulmonary artery trunk (*arrows*) is caused by left main bronchus.

o the shunt, be it truly continuous, or pri-
n rily systolic or diastolic, the velocity of
p monary blood flow is so great in systole
t we could not anticipate a "blanching" sign except during diastole when the blood column is stationary. We should expect, however, that a systolic defect of opacification could be seen at the site of the ostium of the

ductus or that angiographic density studies would show differences in the intensity of systolic opacification of the pulmonary artery along the direction of flow. Only 2 of the 53 patients studied showed an opacification defect during retarded ejection and both of these were of the very large ductus type. Density studies failed to reveal positive evidence of systolic dilution distal to the insertion of the ductus.

The classical concept of continuous shunting with systolic predominance has been questioned in the early phonocardiographic studies of Routier.[29] Recently, Luisada[31] stated, "when the ductus is small, the passage of blood takes place *only* during the last part of systole and slightly afterwards."

Direct visualization of the ductus during left heart opacification after peripheral angiocardiography has been reported by Wegelius and Lind[15] and Hilario, Lind, and Wegelius.[32] The examinations were carried out at high-exposure frequencies, but it is interesting that the ductus was opacified sufficiently to be recognized only on the films made during ventricular diastole.

These findings led us to suspect that the shunt though very likely continuous, is predominantly diastolic. A plausible, and readily acceptable explanation of our concept is not available. However, we have postulated 2 factors that theoretically might influence blood flow through the ductus in such a manner as to produce a predominantly diastolic shunt.

The first is *mechanical* and is caused by the systolic forces acting on the pulmonary artery and aorta in different ballistic vectors. These forces could stretch or twist the ductus sufficiently to produce functional systolic narrowing. In support of this hypothesis are the observations of Janker[33] and later of Teramo,[34] who observed an exaggerated lateral movement of the pulmonary artery in cases of patent ductus arteriosus studied by cinefluorography. We too have observed this movement. Kjellberg and associates[5] intimated that the aortic movements can be transmitted to the pulmonary artery, necessarily, we comment, by the intermediary ductus.

The second factor is *hemodynamic* and is a result of the increased velocity of the aortic flow, which may influence the flow through the ductus by a *Bernoulli-like effect* during systole.[35, 36] A patient with large patent ductus and pulmonary hypertension was studied by catheterization approximately 1 hour before angiocardiography. A mild pressure gradient between the aorta and pulmonary artery was demonstrated (103 to 97 mm. Hg), which should favor systolic flow from aorta to the pulmonary artery. At cineangiocardiography the shunt could be seen very clearly as it entered the aora during systole in spite of the pressure gradient.

Summary and Conclusions

Fifty-three cases of patent ductus arteriosus were studied by classical methods and by cineangiocardiography. The films obtained were studied by analytic projection. From them hemodynamic data were recorded by angiographic density measurement and the movements of the heart chambers and great vessels were represented graphically by cinecardiometry and cine-electrokymography. The tracings obtained were timed and compared with each other.

The most significant and constant cineangiocardiographic signs of the anomaly were the cyclic diastolic loss of density of the pulmonary artery (blanching sign) during the right angiocardiogram and the reopacification of the pulmonary artery during the left angiocardiogram.

Both were attributed to a shunt coming from the aorta into the pulmonary artery via the ductus during diastole.

The degree of "blanching" was not proportional to the amount of the shunt as calculated by the Fick method.

Angiographic density tracings of the pulmonary artery demonstrated that the blanching occurred at the time of the dicrotic wave and increased during diastole. The degree of dicrotism was roughly proportional to the degree of the "blanching" thus proving the relationship of these abnormal movements of the pulmnary artery to the diastolic component of the shunt.

This diastolic component is demonstrated by the blanching of the pulmonary artery, because in that phase the velocity of the pulmonary arterial flow approaches its minimum value, permitting the retrograde flow of nonoxygenified blood shunted from the aorta. However, since all our methods of investigation failed to demonstrate a systolic component of the shunt in the pulmonary artery, and since support was found in isolated observations reported by others, we advanced a hypothesis for future research that the shunt is represented mainly by a diastolic component, at least during angiocardiographic procedure. Mechanical and hydrodynamic suppositions are offered as possible theoretic explanations.

The presence of other lesions complicating patent ductus arteriosus did not detract materially from the high degree of accuracy of these functional changes in establishing the cineangiocardiographic diagnosis.

Acknowledgment

The authors wish to acknowledge the generous help of Dr. Lee B. Lusted in the preparation of the manuscript.

Summario in Interlingua

Cinquanta-tres casos de patente ducto arteriose esseva studiate per methodos classic e per cineangiocardiographia. Le films obtenite esseva studiate per projection analytic. Ab istos, datos hemodynamic esseva registrate per mesuration angiographic de densitate, e le movimentos del cameras cardiac e del grande vasos esseva representate graphicamente per cinecardiometria e cine-electrokymographia. Le registrationes obtenite esseva chronometrate e comparate le unes con le alteres.

Le plus significative e le plus constante signos cineangiocardiographic del anomalia esseva le cyclic perdita diastolic de densitate del arteria pulmonar (signo de blanchimento) in le curso del obtention del angio cardiogramma dextere, con re-opacification in le curso del obtention del angiocardiogramma sinistre.

Ambe ille signos esseva attribuite a un derivation ab le aorta a in le arteria pulmonar via le ducto in le diastole.

Le grado del "blanchimento" non esseva proportional al quantitate del derivation calculate secundo le methodo de Fick.

Registrationes de densitate angiographic in le arteria pulmonar demonstrava que le blanchimento occurreva al tempore del unda dicrotic e cresceva durante le diastole. Le grado del dicrotismo esseva plus o minus proportional al grado del "blanchimento." Isto provava un relation del movimentos anormal del arteria pulmonar con le componente diastolic del derivation.

Iste componente diastolic es demonstrate per le blanchimento del arteria pulmonar, proque in ille phase le velocitate del fluxo in le arteria pulmonar approcha su valor minimal, lo que permitte le fluxo retrograde del non-opacificate sanguine que es derivate ab le aorta. Nonobstante, viste que omne nostre methodos de investigation non succedeva a demonstrar un componente systolic del derivation in le arteria pulmonar e viste que isolate observationes in reportos per altere autores supportava un tal passo, nos formulava—pro un studio futur—le hypothese que le derivation es representate principalmente per un componente diastolic, al minus durante le manovra angiocardiographic. Theses mechanic e hydrodynamic es presentate como possibile explicationes theoric.

Le presentia de altere lesiones que complicava le patente ducto arteriose non disturbava de maniera notabile le alte grado de accuratia con que iste alterationes functional establiva le diagnose cineangiocardiographic.

References

1. Abbott, M. E.: Atlas of Congenital Cardiac Disease. The American Heart Association, 1936.
2. de Balsac, H.: Communications Aorto-pulmonaires. Traité des Cardiopathies Congénitales. Paris, Masson et Cie., 1954, p. 496.
3. Benn, J.: The prognosis of patent ductus arteriosus. Brit. Heart J. 9: 283, 1947.
4. Lynxwiler, C. P., and Wells, C. R.: Patent ductus arteriosus: a report of 180 operations. South. M. J. 43: 61, 1950.
5. Kjellberg, S., Mannheimer, E., Rudhe, U., and Jonsson, B.: Diagnosis of Congenital Heart Disease. Chicago, Year Book Publishers, Inc., 1955, p. 399.
6. Rushmer, R. F.: Cardiac Diagnosis: A Physiologic Approach. Philadelphia and

London, W. B. Saunders Company, 1955, p. 400.

7. Goldbloom, A., Ferencz, C., and Johnson, A. L.: The problem of differential diagnosis in infants with large hearts and increased blood flow to lungs. Am. J. Dis. Child. **86**: 458, 1953.
8. Boone, J. A.: The problem of coexisting patent ductus arteriosus and pulmonary stenosis. South. M. J. **47**: 683, 1954.
9. Keats, T. E., and Steinbach, H. L.: Patent ductus arteriosus: A critical evaluation of its roentgen signs. Radiology **64**: 528, 1955.
10. Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in congenital heart disease. III. Patent ductus arteriosus. Am. J. Roentgenol. **50**: 306, 1943.
11. Furman, R. A.: Angiocardiography, its use in the diagnosis of patent ductus arteriosus. New England J. Med. **238**: 116, 1948.
12. Dotter, C. T., and Steinberg, I.: Angiocardiography. Ann. Roentgenol. **20**: 199, 1951.
13. Goodwin, J. F., Steiner, R. E., Mounsey, J. P. D., MacGregor, A. G., and Wayne, E. J.: A critical analysis of the clinical value of angiocardiography in congenital heart diseases. Brit. J. Radiol. **26**: 161, 1953.
14. Dotter, C. T., and Steinberg, I.: Angiocardiography in congenital heart disease. Seminar on congenital heart disease. Am. J. Med. **12**: 219, 1952.
15. Wegelius, C., and Lind, J.: The role of the exposure rate in angiocardiography. Acta radiol. scandinav. **39**: 177, 1953.
16. Watson, J. S., Weinberg, S., and Ramsey, G. H.: A 70 mm cinefluorographic camera and its relation to detail. Radiology **59**: 858, 1952.
17. Ramsey, G. H., Watson, J. S., Steinhausen, T. B., Thompson, J. J., Dreisinger, F., and Weinberg, S.: Cinefluorography: A progress report on technical problems, dosage factors, and clinical impressions. Radiology **52**: 5, 1949.
18. Weinberg, S., Watson, J. S., and Ramsey, G. H.: A 16 mm projector for research films. J. Soc. Motion Picture and T.V. Eng. **63**: 196, 1954.
19. Campeti, F. L.: Cinecardiometry and cineelectrokymography. New angiographic techniques for the analysis of cardiac mechanics. Accepted for publication *in* Am. J. Roentgenol.
20. Gramiak, R., Watson, J. S., Ramsey, G. H., and Weinberg, S. A.: The blanching sign of patent ductus. Tr. American Coll. Cardiol. **3**: 122, 1953.
21. Goetz, R. H.: New angiocardiographic sign of patent ductus arteriosus. Brit. Heart J. **13**: 242, 1951.
22. Heyer, H. E., Willis, K., and Eddleman, Jr., E. E.: Great vessels motion. Proceedings of the First Conference on electrokymography. U.S. Public Health Service Publication no. 59, 1950, p. 39.
23. Luisada, A. A.: Pulsations of the pulmonary vessels. Proceedings of the First Conference on electrokymography. U.S. Public Health Service Publication no. 59, 1950, p. 65.
24. Girard, J., LaRoche, M. J. A., and Castelain, G.: Les communications interaigmoido-infundibulaires, formes rares des communications bulbaires congénitales. Presse méd. **49**: 1364, 1941.
25. Edwards, J. E.: Congenital Malformations of the Heart and Great Vessels. *In* Pathology of the Heart, S. E. Gould, Ed. Springfield, Ill., Charles C Thomas, Publisher, 1953, p. 439.
26. Cazin, L.: Communications congénitales entre l'aorta et l'A.P. sans persistence due canal artérial. Thése de Paris, 1897.
27. Dexter, L.: Cardiac catheterization. Modern Med. **15**: 96, 1949.
28. Dadds, J. H., and Hoyle, C.: Congenital aortic septal defect. Brit. Heart J. **11**: 390, 1949.
29. Routier, D.: Remarques sur les signes d'auscultations dans P.D.A. Arch. mal coeur **30**: 388, 1937.
30. Perelman, H., and Putschar, W. G. L.: Congenital communications between aorta and pulmonary artery. Internat. A. M. Museums Bull. **30**: 1, 1949.
31. Luisada, A. A.: Heart, Ed. 2, Baltimore, Williams & Wilkins Company, 1954, p. 294.
32. Hilario, J., Lind, J., and Wegelius, C.: Rapid biplane angiocardiography in the tetralogy of Fallot. Brit. Heart J. **16**: 109, 1954.
33. Janker, R.: Der offene Ductus Botalli in Roentgenkinefilm. Fortschr. Röntgenstr. **75**: 79, 1951.
34. Teramo, M.: Valori e limiti della roentgenangiocardiocinematografia nelle cardiopatie congenite. Nuntius radiol. **20**: 835, 1954.
35. Rodbard, S.: Flow through collapsible tubes: Augmented flow produced by resistance at the outlet. Circulation **11**: 280, 1955.
36. —: A study of hydraulics in simulated patent ductus arteriosus. Circulation Research **3**: 613, 1955.

Acute Myocardial Infarction Revealed in an Isolated Premature Ventricular Beat

By KERMIT H. KATZ, M.D., MORTON S. BERK, M.D., AND CHAIM I. MAYMAN, M.D.

Electrocardiograms of 2 patients, suspected instances of acute myocardial infarction, offered an early diagnostic clue in that there were isolated premature ventricular beats manifesting the characteristic changes produced by infarction of the myocardium. In each instance these features were present before the remainder of the electrocardiographic record was conclusive.

THE electrocardiogram is the most consistently useful diagnostic tool in the identification of myocardial infarction. Over 90 per cent of instances of myocardial infarction permit diagnosis by conventional electrocardiographic technics at some time during the clinical course. There remains, however, a small group of patients in which electrocardiographic changes are not sufficiently marked, or do not occur promptly enough to be helpful in making an early diagnosis. Any diagnostic clue afforded by the electrocardiogram that would diminish the size of this group of patients could be very useful.

Recently we encountered such a diagnostic precursor in 2 patients, simultaneously hospitalized, who were suspected of having acute myocardial infarction, but whose electrocardiograms on admission were not conclusive. In each instance, typical changes of early myocardial infarction (prominent Q wave, elevated S-T segment, inverted T wave) were not present in the dominant rhythm, but were apparent in a premature beat. As the evolution of serial electrocardiographic tracings proved, the configuration of these premature beats was adequate to permit a diagnosis of myocardial infarction.

CASE REPORTS

Case 1. While lying in bed in the hospital on January 1, 1958, 1 month after fracturing her hip and undergoing insertion of a Smith-Petersen nail, an 81-year-old woman experienced precordial aching of increasing severity with radiation to the back and down both arms to the fingertips. Apart from slight nausea, she disclaimed any other symptoms. Digitalis was being administered because of mild congestive heart failure.

On examination, frequent premature beats were noted. The heart sounds were normal; there were no murmurs or a friction rub. There were no signs of congestive failure. An electrocardiogram (fig. 1) on January 1, 1958 revealed sinus arrhythmia, atrial and occasional ventricular premature beats. The S-T segments were depressed in leads II, III, and aV_F, and elevated in leads aV_L and V_2. In lead V_2 a conspicuous premature ventricular beat manifested a deep Q wave, marked elevation of the S-T segment, and late inversion of the T wave.

The next day the temperature rose to 100 F. The heart sounds became distant and there were no premature beats. On January 3, 1958 a cardiac friction rub was audible in the fourth intercostal space near the left sternal border. An electrocardiogram (fig. 2) taken at this time revealed the T waves to be isoelectric in lead I and inverted in the left precordial leads. In lead V_3 there was a small broad Q wave with marked elevation of the S-T segments and terminal inversion of the T waves.

On January 14, 1958 an electrocardiogram (fig. 3) showed advanced changes characteristic of the evolution of the pattern of acute myocardial infarction.

The patient required several doses of opiates during the first 72 hours after the onset of chest pain, but she recovered slowly thereafter.

Case 2. A 63-year-old white widow entered the Boston City Hospital on January 3, 1958 because of severe, squeezing, retrosternal pain, radiating down the arms, of several hours' duration. Two years previously the patient had experienced protracted chest pain, and was kept in bed for 2 weeks. Subsequently, she had become progressively limited in her physical activities by dyspnea and by recurrent, oppressive chest pains.

Examination showed rales at the right lung base

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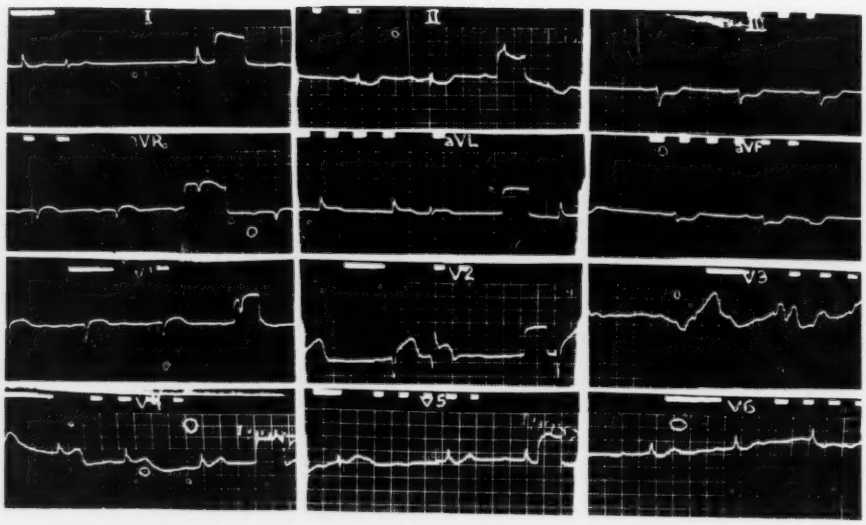


FIG. 1. The single premature ventricular beat in lead V_2 has a deep Q wave, marked elevation of the S-T segment, and late inversion of the T wave.

and occasional premature beats. There were no thrills or rubs. The sedimentation rate was 44 mm. per hour (Wintrobe). The white blood cell count was 12,200, with 84 per cent neutrophils and 16 per cent lymphocytes. The serum glutamic oxalacetic transaminase level was 82 units. A roentgenogram of the chest showed bilateral increase in the bronchovascular markings. The heart size was at the upper limit of normal. The aorta was elongated. An electrocardiogram (fig. 4) taken on entry showed a moderate number of premature beats, sometimes resulting in bigeminy. Deep Q waves were present in leads III and aV_F. S-T segments were depressed in leads I, II, aV_L, and the left precordial leads. In leads aV_F and V_1 there were ventricular premature beats with prominent Q waves and very high take-off of the S-T segments. In an electrocardiogram (fig. 5) 3 days later the T waves in leads III and aV_F were inverted.

Because of gradually increasing pulmonary edema, the patient was digitalized about 12 hours after admission. One week after entry, the patient had a recurrence of severe anterior chest pain requiring treatment with morphine. Electrocardiograms showed transient left bundle-branch block. At this time treatment with heparin was begun. The patient's subsequent clinical course was relatively uneventful until February 2, 1958, 1 month after admission, when she was observed to become suddenly pale and weak, with no perceptible pulse or blood pressure. In a matter of minutes the patient had died.

At postmortem examination there was extensive healing of a relatively recent myocardial infarction, with more recent extension, involving the greater portion of the interventricular septum and posterior left ventricular wall—from base to apex. Over the posterior aspect of the left ventricle was a fibrinous pericarditis. There was focal fibrosis of the left ventricular myocardium. The coronary arteries showed marked atherosclerosis, with segmental old occlusions of the right coronary artery and the left circumflex branch of the left coronary artery.

DISCUSSION

Dressler[1] and Simonson et al.[2] each reported an instance of characteristic changes in ventricular premature beats pointing to the diagnosis of myocardial infarction that was not otherwise detectable by electrocardiogram because of the pattern of bundle-branch block. Scherf and Schott[3] discussed this phenomenon and added an instance in which the diagnosis was dependent upon the characteristic appearance of an atrial premature beat.

The finding of the electrocardiographic pattern of myocardial infarction in a premature ventricular beat in one of our cases led to the detection of the same phenomenon in the other. Inasmuch as premature ventricular beats are expected to be bizarre in appearance, no detailed attention is consistently

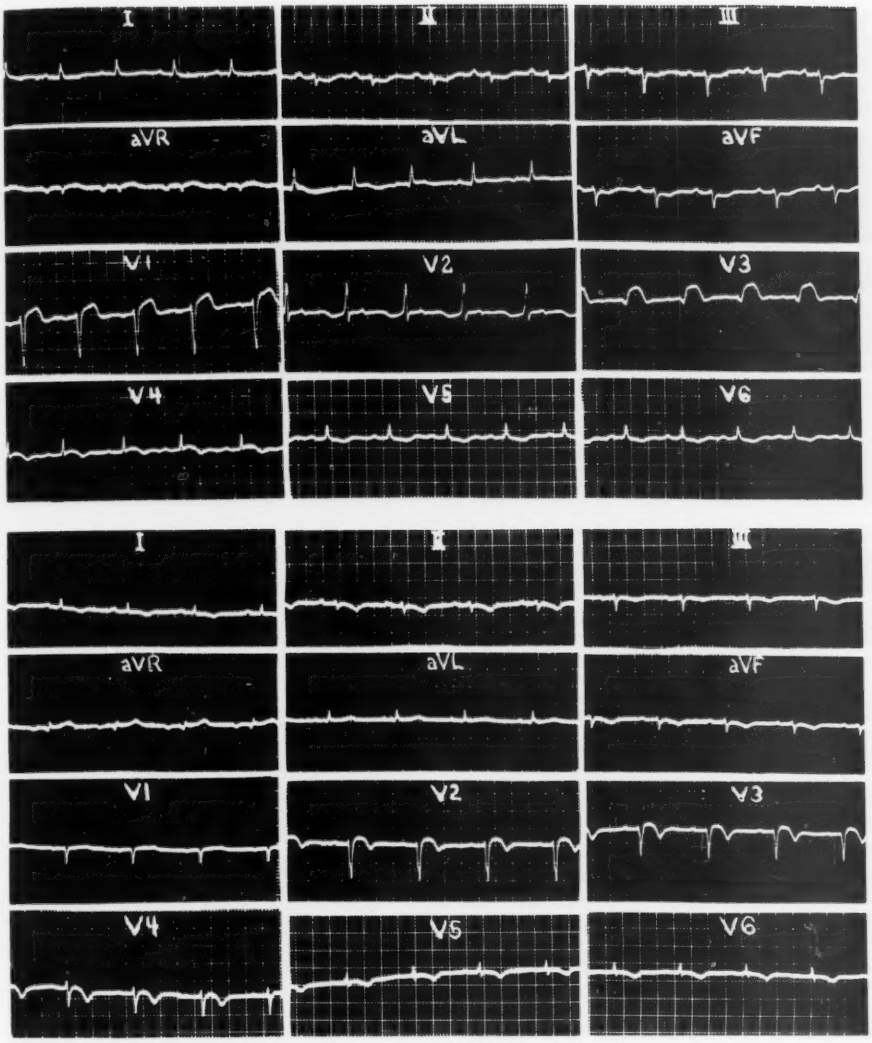


FIG. 2 *Top.* Changes from the previous electrocardiogram include inversion of the T waves in leads $V_{4\text{-}6}$. In lead V_3 there is a small, broad Q wave and marked elevation of the S-T segments.

FIG. 3 *Bottom.* Two weeks after the onset of symptoms the electrocardiogram now shows many characteristics of acute myocardial infarction of the anterior wall of the left ventricle. T waves are inverted in the 3 bipolar limb leads and in leads $V_{2\text{-}6}$. R waves are rudimentary in the right precordial leads.

given to their configuration. The possibility suggests itself that this phenomenon might be more frequently encountered if clinicians were alert to it.

Premature beats, as commonly encountered, show the configuration of a bundle-branch block ventricular complex. The T wave is usually directed opposite to the main deflection of the QRS complex. If an S-T segment is present, as is usually the case, it is dis-

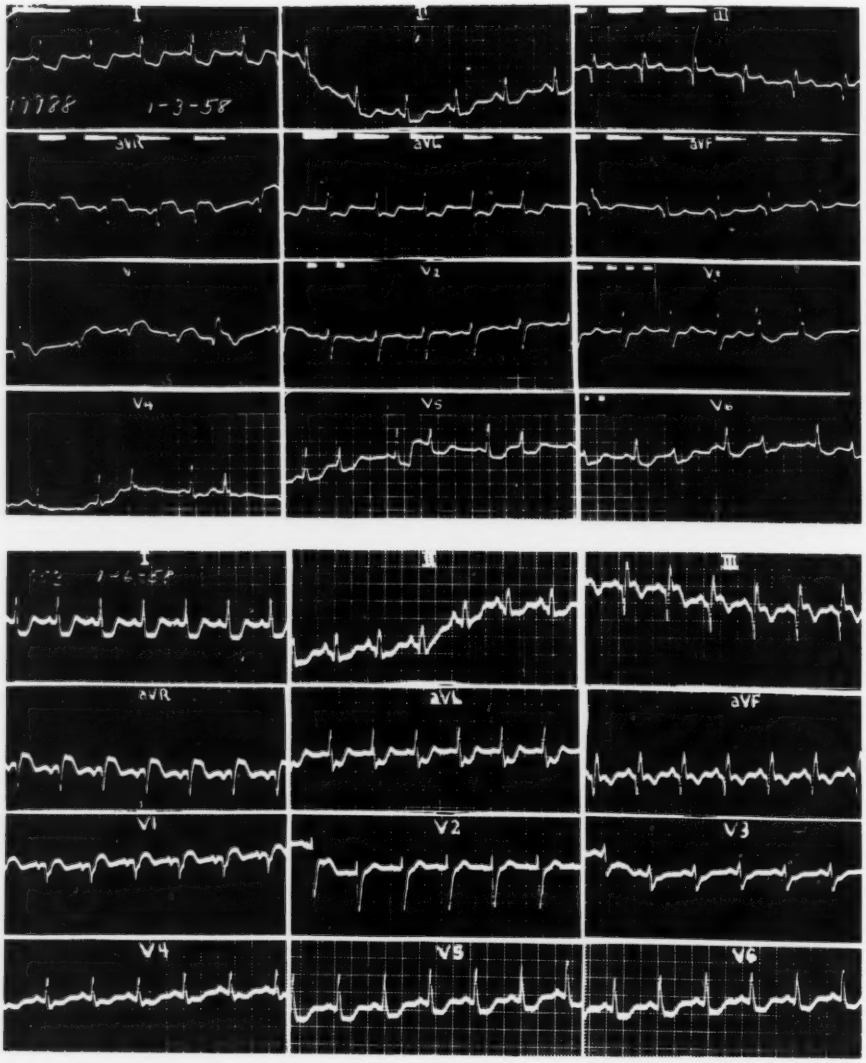


FIG. 4 *Top.* Similar premature ventricular beats in leads aV_F and V_1 show prominent Q waves, elevation of S-T segments and inversion of T waves. Q waves are present in leads III and aV_F.

FIG. 5 *Bottom.* There are marked changes from the previous electrocardiographic record, with deep inversion of T waves in leads III and aV_F, consistent with the evolution of an active process involving the posterior wall of the left ventricle.

placed in the direction of the T wave. In the cases here reported Q waves were prominent, and although the T waves were directed opposite to the main deflection of the QRS complex, the S-T segments were elevated and displaced opposite to the direction of the T waves.

In neither of the 2 cases here presented was there any difficulty in judging, on several bases, that the patients suffered from serious

coronary artery disease. In case 1, however, because of the patient's prolonged period of inactivity and her preceding operation, the possibility of the sudden onset of chest pain being a manifestation of pulmonary embolism was initially considered. The finding of a pattern of myocardial infarction in the premature ventricular beat, before the remainder of the electrocardiogram would permit this diagnosis, suggests its value in more obscure clinical problems.

In case 2, although there was no question as to the presence of coronary artery disease, it was possible to contend—early in her hospitalization—that the findings in the initial electrocardiogram were those of acute coronary insufficiency, superimposed upon the signs of old myocardial infarction, rather than of acute myocardial infarction. Here the significance of the single premature ventricular beats, showing the configuration encountered in acute myocardial infarction, was decisive.

Summary

Two cases are reported in which the correct diagnosis of acute myocardial infarction was made possible by characteristic electrocardiographic features of infarction in isolated premature ventricular beats. These findings were present before the dominant electrocardiographic pattern became completely characteristic of the disease. It is suggested that the phenomenon here reported might be encountered more frequently as an early electrocardiographic evidence of acute myocardial infarction if clinicians were alert to its significance.

Summario in Interlingua

Es reportate duo casos in que le correcte diagnose de acute infarcimento myocardial esseva possibile gratias al characteristic aspecto electrocardiographic de isolate pulsos ventricular prematur. Iste aspecto esseva presente ante que le dominante configuration electrocardiographic deveniva completemente characteristic del morbo. Es opinate que le phenomeno hic reportate va possibilemente incontrar se in plus frequente occasiones si le clinicos es rendite conscie de su signification.

REFERENCES

1. Dressler, W.: A case of myocardial infarction masked by bundle branch block but revealed by occasional premature ventricular beats. Am. J. M. Sc. **206**: 361, 1943.
2. Simonson, E., Enzer, N., and Goodman, J. S.: Coronary insufficiency revealed by ectopal nodal and ventricular beats in the presence of left bundle branch block. Am. J. M. Sc. **209**: 349, 1945.
3. Scherf, D., and Schott, A.: Extrasystoles and Allied Arrhythmias. New York, Grune & Stratton, Inc., 1953.

The Coronary Arteries. A few essential points in the anatomy and physiology of the heart may here engage our attention for a few minutes. The coronary arteries are the Abana and Pharpar of the vascular rivers, "lucid streams," which water the very citadel of life.—William Osler, M.D. *Lectures on Angina Pectoris and Allied States*, 1897.

Supravalvular Aortic Stenosis

By J. J. Denie, M.D., and A. P. Verheugt, M.D.

A case of supravalvular aortic stenosis is described. The diagnosis was suspected from pressure curves obtained at retrograde catheterization of the left ventricle. At operation a circular narrowing of the aorta 2 cm. above the valvular ring was seen. No attempt at surgical correction was made; the patient died at the end of the operation.

ANOMALIES consisting of supravalvular partial occlusion of aortic flow seem to occur very seldom.[1-12] Clinically they are very difficult to distinguish from aortic valvular or subvalvular stenosis. As the surgical resection of the aortic stenosis becomes more commonplace, however, these anomalies may well be encountered more frequently.

Case Report

A murmur was first heard in 1940 by a school physician when the patient was 8 years old. At the age of 19 the boy complained of easy fatigue. In 1951 a harsh systolic murmur, grade III to IV, was heard at the second right interspace near the sternum; it was accompanied by a thrill over the cervical vessels. A diastolic murmur was not heard. A rather loud second aortic sound was noted. The electrocardiogram displayed an R wave in V_2 and V_3 that was much smaller than in V_1 (fig. 1). The roentgenogram showed a double aortic impression in the barium-filled esophagus. A venous angiocardiogram excluded gross anomalies of the aortic arch. A diagnosis was made of aortic stenosis, possibly subvalvular.

In January 1957 serious anginal discomfort and palpitation after very little exertion appeared. The patient was admitted to our hospital ward on August 29, 1957. On examination we found a debilitated young man (25 years), with some degenerative stigmata, such as long slender fingers and toes, prognathism, and thoracic kyphosis. He was 159 cm. tall and weighed 45.5 Kg. At the second right interspace we heard a grade V harsh systolic murmur, radiating to the carotid arteries, accompanied by a very evident carotid shudder. At the third left interspace a holodiastolic decrescendo murmur was heard. The phonocardiogram showed a diamond-shaped systolic murmur, ending just before a second sound of great amplitude. The electrocardiogram showed QS complexes from V_2 to V_5; in V_7 and V_8 the pattern of left ventricular hypertrophy and strain was evident (fig. 2). A roentgenogram of the thorax showed a rounded apex, but the heart seemed rather small (fig. 3). Catheterization of the right heart revealed no shunts and showed slightly raised systolic pressures. By retrograde catheterization of the left ventricle from the right brachial artery we obtained in duplicate a very interesting tracing (fig. 4). Superimposing the aortic on the ventricular tracing, we obtained a systolic gradient of about 90 mm. Hg. The aortic tracing seemed to rule out any serious valvular insufficiency (fig. 5). The aortic valvular area was calculated to be 0.4 $cm.^2$, by means of the modified formula of Gorlin and Gorlin, aortic regurgitation being neglected. A diagnosis was made of aortic stenosis, probably of congenital origin. Antistreptolysin titers were repeatedly less than 100 units. Serologic tests for syphilis were negative. Although some points seemed still unexplained, we decided on surgical intervention with the aid of hypothermia.

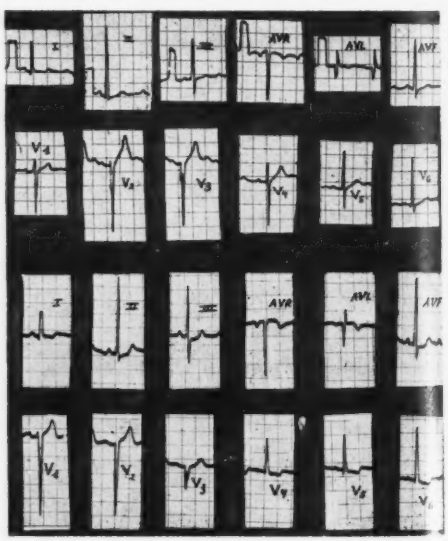
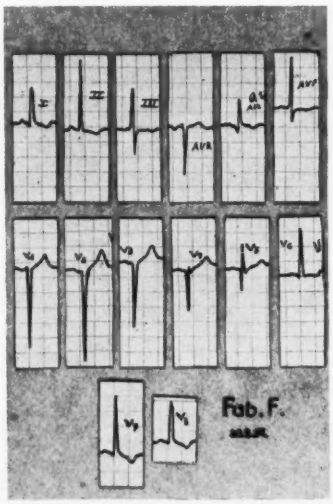
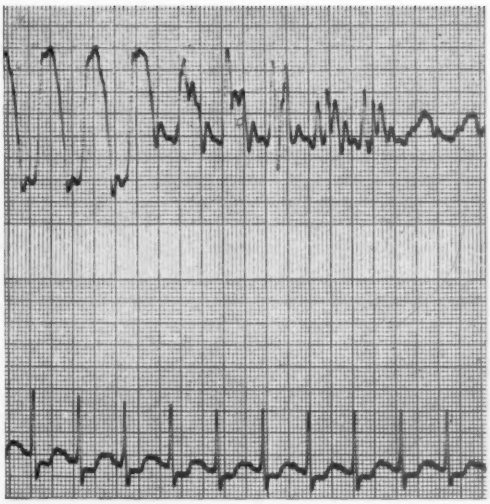
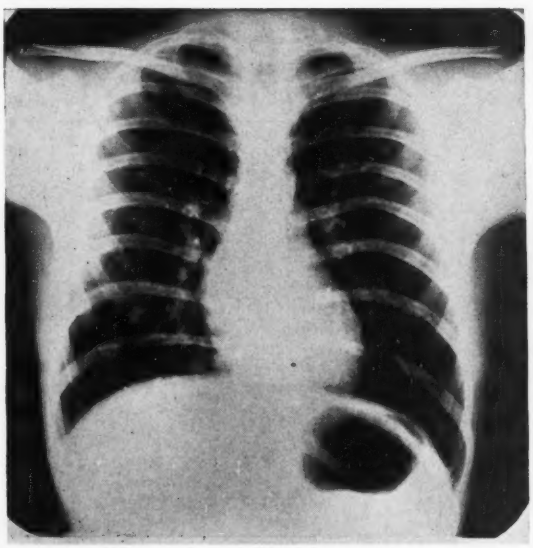


Fig. 1. Electrocardiograms taken December 20, 1951, and January 31, 1957. Note progressive changes.

From Onze Lieve Vrouse Gasthuis, Amsterdam, The Netherlands.







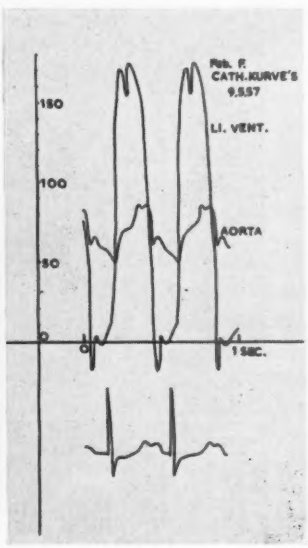


FIG. 2 *Top, left.* Electrocardiogram before surgery. QS complexes evident.

FIG. 3 *Bottom, left.* Roentgenogram of chest before surgical intervention. Note rounded apex. No distinct poststenotic dilatation of the aorta is seen.

FIG. 4 *Top, right.* Pressure curve obtained on withdrawal of the catheter (no. 5, Cournand) from the left ventricle to the aortic arch.

FIG. 5 *Bottom, right.* Pressure curves superimposed. Aortic valve area was calculated from area between these 2 curves.

At thoracotomy on September 10 the surgeon noted a distinct circular narrowing of the aorta immediately distal to the valvular ring. We made pressure tracings from the left ventricle, the aorta, and the area between the aortic cusps and the stenosis (fig. 6). The last tracing shows no great systolic gradient compared with the left ventricular tracing, but a significant lowering of the diastolic pressure. As this type of stenosis seemed inoperable, the thorax was again closed. As the last skin

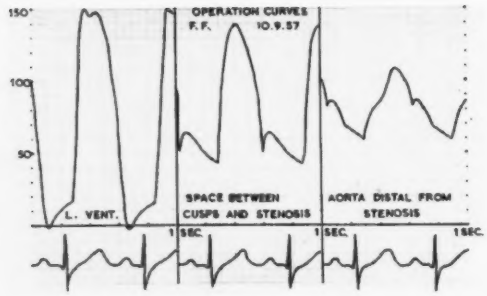


FIG. 6. Curves obtained at operation.

sutures were being placed, the electrocardiogram showed a very pronounced depression of the S-T segments and the arterial pressure decreased to 40 mm. Hg systolic. The thorax was opened again rapidly whereupon ventricular tachycardia began, which rapidly changed to ventricular fibrillation that could not be corrected.

At autopsy the heart was removed in toto. The circular narrowing of the aorta was distinctly seen (fig. 7). By dividing the aorta transversely above the stenosis, the rather narrow aortic lumen came into view (fig. 8). The stenotic area measured about 0.5 cm.^{2}. The stenosis was accentuated by 2 features: a circular narrowing at the level of the insertion of the commissures and a hypertrophy of the plica which normally forms the margin of the sinus of Valsalva. The cusps themselves were of normal size. There was no fusion between the cusps, except at the very outer edge near the commissures. The right coronary artery originated normally in the right sinus of Valsalva. The left coronary artery originated in a blind pouch formed by the fusion of the free margin of the left aortic cusp with the aortic wall. This pouch communicated with the free aortic lumen via a narrow opening. The coronary arteries were otherwise normally permeable (fig. 9). The pulmonary artery and the

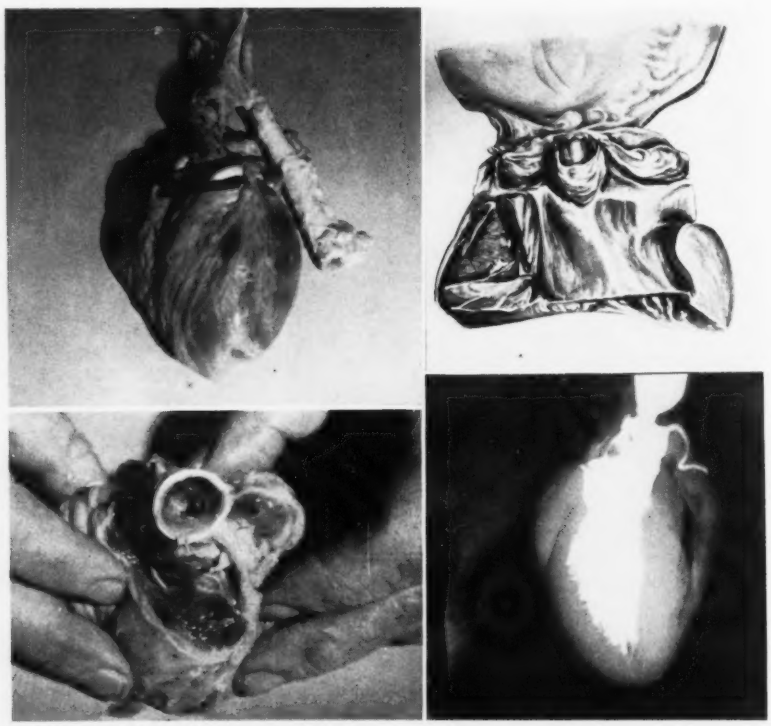


FIG. 7. Heart. Local circular narrowing of aorta is shown.

FIG. 8. View after transverse division of aorta.

FIG. 9. The fixed preparation. Aorta has been cut between left and noncoronary cusps.

FIG. 10. Roentgenogram obtained after filling the specimen with barium contrast medium. Right coronary artery is distinctly shown, left is barely filled.

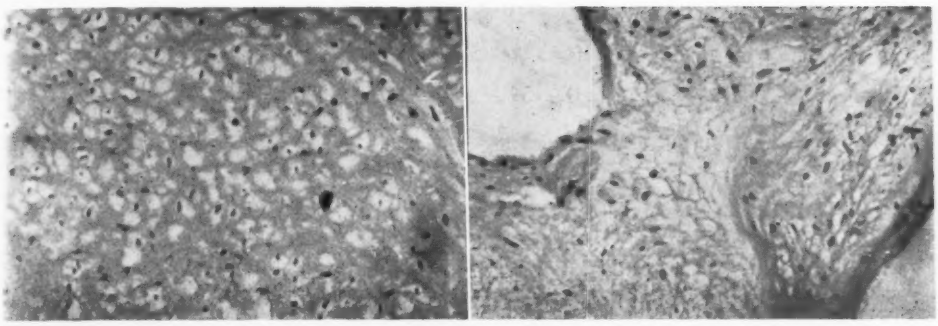


FIG. 11 *Left.* Microscopic anatomy of media at height of stenosis. Note distinct cystic degeneration.

FIG. 12 *Right.* Microscopy of fusion between left aortic cusp and aortic wall; no inflammatory changes.

right ventricle were normal. The myocardium of the left ventricle was greatly hypertrophied. Roentgenograms of the specimen with barium contrast medium showed very clearly the cusps and supravalvular stenosis. The left coronary artery was very poorly filled (fig. 10).

On microscopic examination the aortic wall just above the cusps showed a distinct hypertrophy of the media, which was most pronounced at the height of the stenosing ring. Except for this hypertrophy of the media, the aortic wall in this area showed no gross changes, in particular no leukocytic infiltration or Aschoff bodies. There appeared a slight grade of mucoid degeneration of the media that resembled that seen in cystic medial necrosis (fig. 11). This mucoid degeneration extended over a short distance along the media of the coronary arteries. At the fusion of the left cusp with the aortic wall there were no distinct inflammatory reactions (fig. 12). A small atrophic muscular bundle ran from the more ventral to the more dorsal commissure in the left aortic cusp a few millimeters from the line of fusion (fig. 13). The aortic wall 3 cm. above the stenosis showed no abnormalities. The myocardium of the left ventricle showed an advanced stage of fibrous myocarditis.

DISCUSSION

The origin of the lesion seems to be congenital. Clinically there are no reasons to suspect a rheumatic etiology. There is probably a relation between the mucoid degeneration and the constitutional type of patient, which in certain points resembles that of the Marfan syndrome. The fusion of the left cusp with the aortic wall explains the anginal complaints, the electrocardiographic changes, and the ventricular fibrillation at the end of the surgical intervention. The aortic regurgitation was also caused by this particular feature. We consider that this fusion developed gradually and is correlated with the progressive electrocardiographic changes and the rather abrupt onset of very severe anginal complaints. The fact that the very evident auscultatory signs of aortic regurgitation were not perceived at the first examination of the patient in 1951 would also point to this conclusion. The microscopic examination, however, does not confirm this supposition.

The pressure curves show some interesting peculiarities. Superimposing the aortic curve and the left ventricular curve obtained at operation, we see that the dicrotic notch of the aortic curve falls distinctly by a time interval of 0.02 second after the descending branch of the left ventricular curve (fig. 14). This is easy to understand when we realize that the dicrotic notch of the aortic curve is located on a higher pressure level than the notch of the curve obtained between aortic valve and stenosis. This last curve shows also a lower diastolic level and a much steeper descent than the aortic arch curve. It seems that the stenosis minimized the aortic regurgitation. When we observed these 2 features more closely of a lower diastolic level just after the cusps and a dicrotic notch in the aortic curve that falls after the descending branch of the left ventricular curve, we no-

TABLE 1.—*Survey of Reported Cases*

Author and reference no.	Age/Sex	Description	Place of obstruction	Clinical findings	Cause of death Associated anomal
Archer (1)	M 39	Band, 1.3 cm. long with free edges	Just above insertion of aortic cusps	Autopsy finding	
Brody (2)	M 24	Band with free edges	Just above insertion of cusps	Autopsy finding	Patent foramen ovale. Ductus arteriosus persist
Burry (3)	W 37	(1) Circular narrowing of aorta with (2) Two ridges	(1) Just above the cusps at the upper margin of sinuses of Valsalva (2) Between commissures above left and anterior cusp	No murmurs recorded. Physical signs of Marfan syndrome	Died of congenita failure. Small ap myocardial infarc tion with endocard thrombosis. Deepe ing of sinuses of Valsalva. Narrowi of aperture of left sinus of Valsalva
Kretz cited by Hektoen (5)	—	Two fibrous bands across lumen of aorta	Just above insertion of aortic cusps		
Lev (6)		Circular narrowing of aorta	At the level of the entry of the sinuses of Valsalva		
Luksch (7)	M 76	Tendinous chord across lumen of aorta	2-3 cm. above aortic cusps	Autopsy finding	
Mönckeberg (8)	M 26	Circular narrowing of aorta	1-2 cm. above valvular ring	Those of aortic coaretation	Short aortic arch, aortic coarctation. Died of rupture of aneurysma below coarctation
Nikiforoff (9) cited by Rohrle	Infant	Band with free edges in the lumen of aorta	Between commissure of left and noncoronary and commissure of left and right cusp	Autopsy finding	
Rohrle (9)	2 weeks	Band with free edges in the lumen of aorta	Between commissure of left and noncoronary and commissure of left and right cusp	Autopsy finding	Died of colitis
Rosenberg (9) cited by Rohrle	M adult	Band with free edges in the lumen of aorta	Between commissure of left and noncoronary and commissure of left and right cusp	Musical systolic murmur aortic region	
Stephen (10)	M 30	Stenosing membrane in lumen of aorta	Inserting at the height of the commissures, fused with lunulae of noncoronary and right cusp	Those of aortic stenosis and aortic regurgitation. The regurgitation was caused by fusing of the left and noncoronary cusps with the membrane	Abdominal blind pouch in which originated a thrombus. Died of congestive failure
Torres and Calvacanti (11)	M 32	Band with free edges across aortic lumen	Between commissure of left and noncoronary and commissure of left and right cusps	Systolic and diastolic aortic murmur	Atrophy of left aortic cusp. Died of congestive failure
Torres and Calvacanti (11)	Stillborn	Band with free edges across aortic lumen	Between commissure of left and noncoronary and commissure of left and right cusps		
Weinstein (12)	M 50	Anomalous band across lumen of aorta	2 cm. above the cusps		Atrophy of left aortic cusp. Died o intestinal obstructi

Fig. 13. In left aortic cusp muscular elements were found running a few millimeters from the aortic wall.

tioned that both were already present on our pressure curves obtained at catheterization (figs. 4 and 5). In analogy with subvalvular stenosis and in accord with other authors,[3, 4, 6] we classify this case as supravalvular stenosis. That a supravalvular stenosis indeed may occur, is not generally known. We can roughly divide the recorded cases in 2 groups (table 1). The first comprises membranous chords (with muscular elements), or membranes that protrude in the free aortic lumen, a second group local narrowing of the aorta in the ascending part.

The cases of Nikiforoff, Rorhle, and Rosenberg (cited by Rorhle[9]), the 2 cases of Torres and Calvacanti[11] show the same localization of the supravalvular aortic band. This band runs from the commissure between the left and noncoronary aortic cusp and the commissure between the left and right aortic cusp. It is most remarkable that in our case upon microscopic examination a muscular band was found in the left deformed cusp which showed approximately the same localization. It seems then that in our case both of the previously described mechanisms are involved. The recorded physical signs are those of aortic valvular stenosis, mostly accompanied by those of aortic insufficiency. Sometimes the peculiar musical quality of the aortic systolic murmur is noted. Except for a loud second aortic sound, there seem to be no physical signs that permit a distinction between a supravalvular and a valvular stenosis. Curves as obtained by retrograde left ventricular catheterization

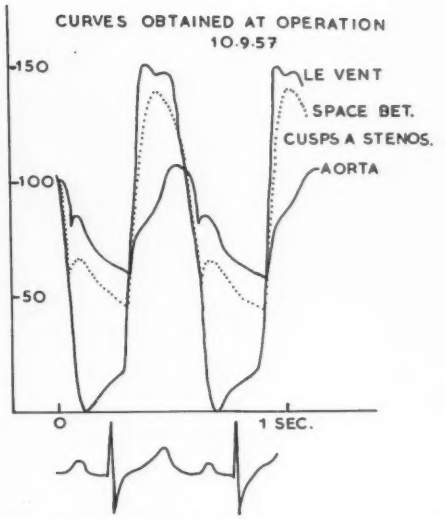


Fig. 14. Superimposed tracings obtained at operation. Incisura of aortic arch curve retarded in respect to descending limb of left ventricular curve.

should, when examined closely, contain important clues for the diagnosis of either subvalvular or supravalvular stenosis.[4] With the aid of aortography it would probably have been possible in our case to locate the site of the stenosis more accurately.

Summary

A case is described of supravalvular aortic stenosis that was suspected on clinical examination and was confirmed by surgery. The Marfan habitus of the patient correlated with the mucoid degeneration of the media found at microscopic examination. Certain peculiarities in the curves obtained at catheterization and at surgery are discussed. A review is presented of 14 cases confirmed by autopsy.

Acknowledgment

We wish to express our appreciation to Dr. A. Schaepkensvan Riempst and Dr. A. Gründemann who performed the operation and allowed us to use their data. May we further thank Dr. H. van der Linden for his cooperation in providing the autopsy material.

Summario in Interlingua

Es describite un caso de stenosis aortic supravalvular. Le presentia del condition

esseva suspicite al examine clinic e confirmate al operation. Le habitus Marfan del patiente esseva in correlation con le degeneration mucoide del media, trovate al examine microscopic. Es discutite certe peculiaritates in le curvas obtenite al catheterisation e al operation. Es presentate un revista de 14 casos, omnes necropticamente confirmate.

REFERENCES

1. Archer, R. S.: Note on a congenital band stretching across the origin of the aorta. Dublin J. M. Sc. **65**: 405, 1878.
2. Brody, H.: Congenital cord across the origin of the aortic valve. J. Tech. Methods **22**: 110, 1942.
3. Burry, A. F.: Supra-aortic stenosis associated with Marfan's syndrome. Brit. Heart J.. **20**: 143, 1958.
4. Gründemann, A. M.: Retrograde catheterisation of left ventricle. In press.
5. Hektoen, L.: Rare cardiac anomalies. Tr. Chicago Path. Soc. **4**: 97, 1899-1901.
6. Lev, M.: Autopsy Diagnosis of Congenital Malformed Hearts. Springfield, Ill., Charles C Thomas, 1953, p. 53.
7. Luksch, F.: Über einen querverlaufenden Strang in der Aorta ascendens. Zentralbl. allg. Path. **23**: 626, 1912.
8. Mönckeberg-Gieben: Einige Komplikationen bei angeborener Stenose des Isthmus Aortae. Verhandl. deutsch. path. Gesellsch. 1: 267, 1907.
9. Rohrle, F.: Chorda tendinea congenitalis aorta. Deutsche med. Wchnschr. **22**: 27[illegible], 1896.
10. Cheu, S., Fiese, M. J., and Hatayama, H.: Supra-aortic stenosis. Congenital supra-aortic valvular stenosing membrane on the aortic cusps. Am. J. Clin. Path. **28**: 29[illegible], 1957.
11. Torres, E. T., and Calvacanti, A. R.: Congenital elastic band of aortic valve. Arq. Heart J. **45**: 630, 1953.
12. Weinstein, S.: An anomalous band across the channel of the aorta at the level of the aortic leaflets. Tr. Chicago Path. Soc. 12: 277, 1927.

Riss, E., and Levine, S. A.: Two Cases of Atrial Fibrillation of Many Years' Duration Regularized by Quinidine. Am. J. M. Sc. **233**: 654 (June), 1957.

Atrial fibrillation, usually associated with some form of heart disease, may occur in individuals without evidence of cardiac or other systemic disorders. Two brothers with atrial fibrillation of 17 years' and 5 years' duration were studied. No evidence of heart disease could be detected; in addition, the son of 1 of the brothers was found to have the same condition. Despite the long duration of arrhythmia in these 2 patients, large doses of quinidine were effective in restoring the heart to normal sinus rhythm. Increasing doses of the drug were employed until single doses of 1.5 Gm. and 2.0 Gm. respectively were reached. The drug was withdrawn gradually after reversion to normal rhythm, which had persisted for 5 years and 3 years. The plan used for treatment of atrial fibrillation is that of digitalization for correction of rapid ventricular rates; heparinization to prevent embolization; and careful increasing of the quinidine dosage until revision to sinus mechanism occurs. The drug is stopped immediately if the blood pressure decreases, pulse rate increases, QRS complex widens by 50 per cent or more, or if respiratory difficulty, syncope, or blurred vision develops. A high percentage of fibrillators with normal hearts respond well to quinidine in contrast to the results obtained with such treatment in patients with mitral stenosis.

Shuman

Cardiac Arrhythmias Associated with the Repair of Atrial and Ventricular Septal Defects

By Rikuro Sasaki, M.D., E. O. Theilen, M.D., L. E. January, M.D., and J. L. Ehrenhaft, M.D.

This is a report of cardiac arrhythmias associated with the repair of cardiac septal defects. Electrocardiographic studies showed a high incidence of paroxysmal disturbances of rhythm following surgery.

THE remarkable technics of modern cardiac surgery, that permit restoration of normal anatomic and hemodynamic relationships in hearts with septal defects, have created some problems in the identification and control of postoperative arrhythmias. It is not surprising that auriculotomy and ventriculotomy with the closure of septal defects might produce significant disturbances of cardiac rhythm in view of the proximity of some of the specialized conducting tissues to these defects. Previous reports of surgically treated patients do not stress the occurrence of postoperative arrhythmias. This report is a review of the cardiac arrhythmias that have occurred in a series of 110 patients with atrial (62) and ventricular (48) septal defects operated on before January 1, 1958. A significant proportion of these patients had major disturbances of rhythm in the immediate postoperative period, and in the case of patients with atrial septal defects, various paroxysmal arrhythmias occurred during convalescence. Our patients were monitored electrocardiographically during surgery, at frequent intervals during the first postoperative day, and as often as indicated thereafter.

Atrial Septal Defects

All but 2 of the patients with atrial septal defects were operated on under hypothermic conditions. Rapid surface cooling was induced by immersion of the anesthetized patient in a tub filled with cracked ice and water. Cardiotomy was performed during occlusion of the large vessels of the in-flow and out-flow tracts to permit operation in a bloodless field. Two periods of circulatory occlusion were used when valvular pulmonic stenosis was associated with an atrial septal defect. Pulmonic valvuloplasty was performed during the first and shorter period of occlusion; then the heart was allowed to recover before the second period of occlusion for repair of the atrial septal defect. A modified atrioseptopexy was done in 2 patients with anomalous pulmonary venous connections; in them the circulation was not obstructed because the nature of the anomaly made open cardiotomy and visualization of the defects unnecessary.

Hicks and co-workers[1] and Fleming and Muir[2] have reported the electrocardiographic changes that occur during hypothermia. Similar changes were observed in our patients. Ventricular fibrillation was a frequent complication of cardiotomy under hypothermic conditions, occurring in 25 of 60 patients. The general problem of ventricular fibrillation in hypothermia has been reviewed recently by Badeer.[3] The scattergram (fig. 1) shows that the occurrence of ventricular fibrillation in our series was related not only to the length of circulatory occlusion but also to the extent of body cooling as well. Sinus rhythm was restored in 23 of the 25 patients. It could not be restored in 1 child with an ostium primum

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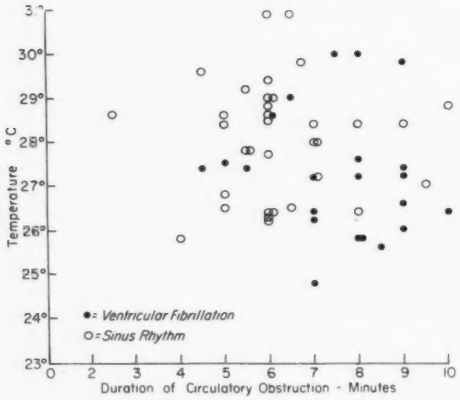


FIG. 1. Ventricular fibrillation occurred in 22 of 56 patients subjected to both hypothermia and temporary circulatory occlusion for repair of atrial septal defects.

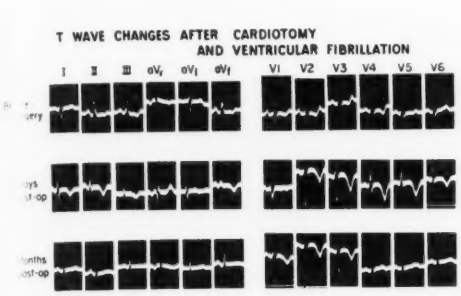
defect and in 1 woman with an associated mitral stenosis. Severe pulmonary hypertension (pressures 80/40 and 95/65) was found in these 2 patients. Defibrillation generally was accomplished with little difficulty, although 6 of the 25 patients maintained the arrhythmia for more than 1 minute. These longer periods of fibrillation were 4, 5, 8, 27, 40, and 120 minutes respectively, despite continued cardiac massage and repeated attempts at electric defibrillation. Sinus rhythm was restored ultimately in each of these 6 patients. Evidence of muscle damage occurred in the 2 patients who fibrillated for 8 and 120 minutes and in 1 who fibrillated for less than 1 minute. The electrocardiographic changes consisted of deep T-wave inversions that gradually regressed (fig. 2). Clinical recovery was complete. It seems likely that more than one factor is responsible for the electrocardiographic evidence of muscle damage after ventricular fibrillation. The duration of the attack, the trauma of cardiac massage, and electric defibrillation are undoubtedly important factors. Peddie et al.[4] have shown that structural changes in the heart may result from cardiac massage.

Preoperative cardiac arrhythmias were not common in these patients. Atrial fibrillation was present in a 44 year old woman with an isolated ostium secundum defect and moderate pulmonary hypertension (67/30 mm. Hg). Paroxysmal supraventricular tachycardia was documented in a 15 year old girl with an ostium primum defect. It is of interest that first-degree atrioventricular heart block (P-R 0.22 to 0.24 second) occurred only in patients with ostium primum defects. It occurred in 4 such patients, aged 10 to 23 years, none of whom had received digitalis.

The frequency of postoperative cardiac arrhythmias was impressive (table 1). Eighteen patients (30.5 per cent) who survived the immediate postoperative period developed disturbances that were not present preoperatively. All were supraventricular in origin. The following arrhythmias appeared during the first postoperative day in 9 patients: paroxysmal nodal tachycardia, 1; atrial fibrillation, 5; atrial flutter, 1; and paroxysmal atrial tachycardia, 2. With 1 exception the arrhythmias during the first day were transient and responded readily to digitalization. The paroxysmal nodal tachycardia occurred in a child who continued to have difficulty for more than 1 year. She had intermittent paroxysms of supraventricular tachycardia associated with faintness and weakness and episodes of paroxysmal nodal tachycardia that alternated with periods of reciprocal rhythm and wandering pacemaker.

Nine patients with complicated atrial septal defects died, 3 in the operating room. Two were the result of persistent ventricular fibrillation; in the other a complete A-V heart block resulted in an ineffective idioventricular rhythm. Five deaths, all in patients who had ostium primum defects, occurred within 48 hours after operation but were not the result of rhythm disturbances. One child in whom a large patent ductus arteriosus was ligated in addition to closure of the atrial defect died 8 days postoperatively of congestive heart failure.

The appearance of paroxysmal arrhythmia sometimes was delayed. Arrhythmias occurred unpredictably from 3 days to 8 months postoperatively. Atrial flutter with a 1:1 response at a rate of 273 per minute



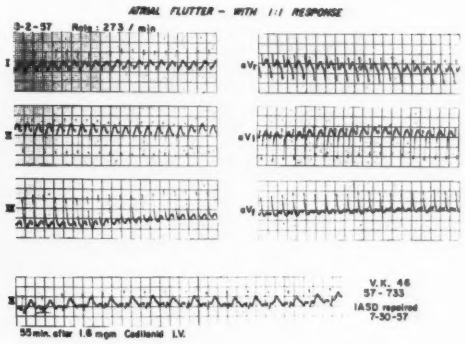


FIG. 2 *Left.* Serial tracings of a 28-year-old woman who had intermittent ventricular fibrillation for 120 minutes following closure of an atrial septal defect. Note the extensive T-wave abnormalities after operation. These changes regressed as shown in the tracing 6 months after operation.

FIG. 3 *Right.* This tachycardia at a rate of 273 per minute occurred on the third postoperative day in a 46-year-old man following repair of an atrial septal defect with anomalous pulmonary venous connections. The rate was halved after digitalis, suggesting that the tachycardia was probably atrial flutter with a 1:1 response.

developed on the third postoperative day in 1 patient who had a modified atrioseptopexy to repair an atrial defect associated with partial anomalous pulmonary venous drainage (fig. 3). Atrial fibrillation appeared 2 weeks after operation in a girl who had an uncomplicated ostium secundum defect. Despite treatment it recurred intermittently and alternated with paroxysmal atrial tachycardia with 3:1 A-V block, a wandering pacemaker, and a nodal rhythm for 3 months before sinus rhythm was re-established and maintained. Two other patients developed short episodes of paroxysmal atrial tachycardia with incomplete A-V heart block 2 to 4 weeks after operation for ostium secundum defects. Neither had received digitalis and neither had other rhythm disturbances. A fifth patient began

TABLE 1.—*Arrhythmias after Repair of Atrial Septal Defects under Hypothermia*

			Postoperative arrhythmias							
					Tachycardias					
Defect	Number	Ventr.fibrill. during operation	Nodal rhythm	A-V heart block	Supra-ventricular	Nodal	Atrial with A-V block	Atrial fibrill.	Atrial flutter	Deaths
Isolated secundum	26	10	7	2	3	1	2	4	1	
Ostium primum	13	9			1					7
ASD with anomalous pulmonary venous connections	8	3						1	1	
ASD with valvular pulmonic stenosis	13	1					1	1	1	
ASD with PDA.....	1	1	1							1
ASD with mitral stenosis..	1	1								1
Total	62	25	8	2	4	1	3	6	3	9

ASD, atrial septal defect; PDA, patent ductus arteriosus.

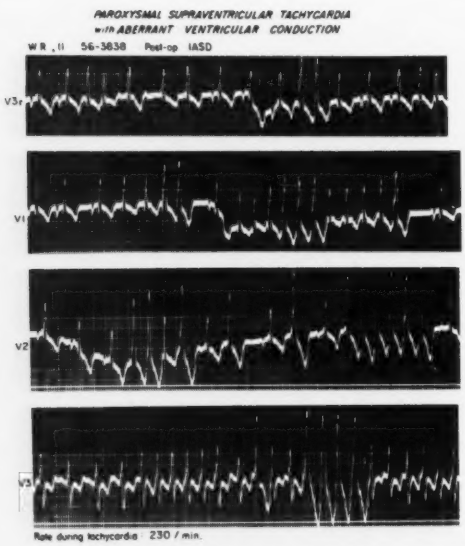


FIG. 4. Right precordial leads in an 11-year-old boy 3 weeks after repair of an atrial septal defect. He complained of a sudden onset of weakness and faintness. This tracing demonstrates bursts of supraventricular tachycardia with aberrant ventricular conduction. Sinus rhythm was restored after digitalization.

having bursts of supraventricular tachycardia with ventricular aberration at rates of 230 per minute (fig. 4) 3 weeks after operation. Sinus rhythm was re-established after digitalization, and he had no further attacks. Two patients with uncomplicated secundum defects developed asymptomatic second-degree A-V heart block 6 weeks and 5 months after operation. They have not required treatment.

Nodal rhythm without tachycardia has been a relatively common finding. It occurred in 5 patients who had no other arrhythmia, and was present intermittently in 3 more who also had other arrhythmias. It has persisted from 1 day to more than 1 year after operation.

The explanation for the supraventricular arrhythmias is unknown. The common denominators have been hypothermia, circulatory occlusion, the incision of the wall of the right atrium, and the placement of sutures for the closure of the atrial defects. There appears to be no correlation with the degree of body cooling, the severity of pulmonary hypertension, or the occurrence of ventricular fibrillation during surgery. Perhaps irritable foci, developing during the healing process of the traumatized atrial tissue, give rise to delayed disturbances of rhythm.

VENTRICULAR SEPTAL DEFECTS

Cardiac-bypass procedures were employed in 46 of 48 patients with ventricular septal defects operated on before January 1, 1958. One was successfully repaired under hypothermia alone. The ventricular septal defect was not closed in 1 child, who also had an atrial defect and valvular pulmonic stenosis, although the latter 2 lesions were corrected under hypothermia. Potassium arrest of the

TABLE 2.—*Arrhythmias after Cardiotomy for Repair of Ventricular Septal Defects (VSD)*

Defect	Number	Potassium arrest	Ventr. fibrill.	Postoperative arrhythmias					Deaths
				A-V heart block	Tachycardias: Supra-ventricular	Tachycardias: Atrial	Tachycardias: Nodal	Flutter-fibrill.	
Isolated VSD									
Membranous septum	26	3	1	2	5	3	2	Flutter 1	1
Muscular septum	2								
VSD with unsupported aortic cusp	2	1	1	1		1			
VSD with tricuspid insufficiency	2	0	2						
VSD with pulmonic stenosis	11	4	4		3	3		Fibril. 1	
VSD with atrial septal defect and pulmonic stenosis	4	2		2			1		
VSD with patent ductus	1	1	1		1				
Total	48	11	9	5	9	7	3	2	1

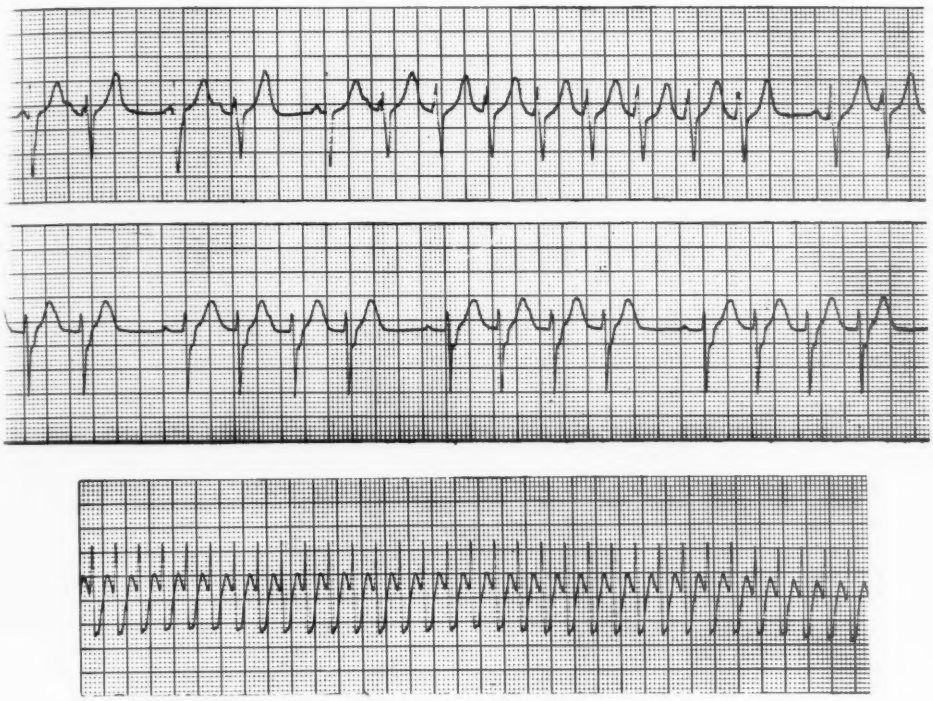


FIG. 5 *Top.* Lead I in a 7-year-old boy and (*bottom*) Lead I on a 4-year-old boy after operation, demonstrating paroxysmal atrial tachycardia at the relatively slow rates of 136 and 139 beats per minute, respectively. These children had ventricular septal defects and infundibular pulmonic stenosis.

FIG. 6 *Bottom.* Lead II in a 5-year-old boy demonstrating supraventricular tachycardia at a rate of 300 per minute. This may be an example of atrial flutter with a 1:1 response. The patient responded to digitalization.

heart in conjunction with a pump oxygenator was used 11 times.

Ventricular fibrillation occurred in 9 patients during closure of the ventricular septal defects. Sinus rhythm was restored easily in all but 1 who died. This arrhythmia occurred in 8 patients operated on with the pump oxygenator, in 3 of whom potassium arrest also was used. The other patient with ventricular fibrillation, whose defect was repaired under hypothermia, was easily defibrillated. Coronary air embolism was thought to be responsible for ventricular fibrillation in 2 patients with potassium arrest. In one, poor contractions were observed first in an area over the free wall of the left ventricle although the remainder of the heart contracted normally; ventricular fibrillation developed a short time later. Vigorous fibrillary contractions developed in the area of the left ventricle that had previously been atonic after cardiac massage, and electric countershock reestablished regular ventricular contractions.

Eight patients died, 1 from ventricular fibrillation at the time of surgery, and 7 others within 48 hours after operation. One, with an isolated ventricular septal defect and severe pulmonary hypertension (75/36 mm. Hg), and 2, who had an atrial septal defect and pulmonic stenosis as well as a ventricular septal defect, developed complete A-V heart block that persisted until death. Arrhythmias were not clearly related to the deaths of the other 4 patients, although supraventricular

tachycardias at rates of 166, 176, and 180 per minute were observed in 3. However, complete A-V block was not always fatal. It occurred 6 hours after operation in 1 patient, but spontaneously reverted to a sinus rhythm several hours later. Complete A-V heart block with ventricular standstill was observed in a patient with associated infundibular pulmonic stenosis when coronary perfusion was restored following potassium arrest. The block disappeared and sinus rhythm returned when a single suture was removed from the muscular tissue near the anterior margin of the defect.

Most patients had sinus tachycardias for 24 to 48 hours after operation. Rates of 140 to 150 per minute in children have been common. However, ectopic pacemakers were definitely established as responsible for the tachycardia in only 2 patients with heart rates in this range (136 and 139 beats per minute, fig. 5). All tracings in which heart rates were in excess of 160 per minute were examined critically. It was not always possible to determine with certainty whether an arrhythmia originated in an ectopic focus or was an extreme sinus tachycardia. The ectopic origin of the arrhythmia could be demonstrated conclusively in a few instances. Nineteen of 48 patients (39 per cent) had supraventricular tachycardia. Heart rates varied from 166 to 200 per minute except for 2 patients with intermittent paroxysmal atrial tachycardia at rates of 136 and 139 per minute (table 2). Rates slower than 160 with identifiable P waves of normal configuration were not considered to be paroxysmal arrhythmias unless there was electrocardiographic proof of the abrupt paroxysmal nature of the tachycardia. One child with an unusually rapid ventricular rate of 300 per minute probably had atrial flutter with a 1:1 response, although definite proof was lacking (fig. 6). All of the surviving patients who had supraventricular tachycardia and 1 with 2:1 atrial flutter responded to intravenous digitalization. Thus far, none of the patients with repaired ventricular septal defects has developed arrhythmias in the late postoperative period, in contrast to those with repaired atrial septal defects.

Summary

Ventricular fibrillation was a frequent complication in the repair of atrial septal defects under hypothermia. It occurred in 25 of 60 patients and was related to the extent of body cooling as well as the length of circulatory occlusion. Restoration of sinus rhythm was accomplished in all but 2 patients who had pulmonary hypertension. Thirty per cent of those patients operated upon successfully for the closure of atrial defects developed supraventricular rhythm disturbances 3 days to 8 months after operation. Supraventricular tachycardias predominated.

Ventricular fibrillation occurred during operation in 9 of 48 patients operated on for ventricular septal defects. Sinus rhythm was restored in all but 1. Coronary air embolism may have initiated ventricular fibrillation in 2 patients. Paroxysmal supraventricular tachycardia responding to digitalization was a common occurrence during the first 24 hours after closure of ventricular septal defects. However, disturbances of rhythm have not appeared later in the convalescent and postoperative period as they have in the patients with atrial septal defects.

Summario in Interlingua

Fibrillation ventricular esseva un complication frequente in le reparo de defectos atrioseptal sub hypothermia. Illo occurreva in 25 ex 60 patientes e esseva relationate con le extension del frigidation del corpore e tetiam con le duration del occlusion circulatori. Restauration del rhythmo sinusal esseva complite in omne le patientes con le exception de 2. Istes habeva hypertension pulmonar. Trenta pro cento del patientes in qui le operation succedeva a clauder le defectos atrial disveloppava disturbationes de rhythmo supraventricular, 3 a 8 menses post le operation. Tachycardias supraventricular predominava.

Fibrillation ventricular occurreva durante le operation in 9 ex 48 patientes con defectos ventriculo-septal. Le rhythmo sinusal esseva

rest rate in omnes con 1 exception. Embolisn aeree coronari initiava possibilemente le rillation ventricular in 2 patientes. Tac cardia supraventricular paroxysmal, que respondeva a digitalisation, esseva un occ rentia commun durante le prime 24 hor post clauditura de defectos ventriculosep . Tamen, per contrasto con le patientes con efectos atrio-septal, nulle operato in iste gru po manifestava disturbationes rhythmic plu tarde, durante le periodo de convalescentia ost-operatori.

REFERENCES

1. Hicks, C. E., McCord, M. C., and Blount, S. G., Jr.: Electrocardiographic changes during hypothermia and circulatory occlusion. Circulation **13**: 21, 1956.
2. Fleming, P. R., and Muir, F. H.: Electrocardiographic changes in hypothermia in man. Brit. Heart J. **19**: 59, 1957.
3. Badeer, H.: Ventricular fibrillation in hypothermia. J. Thoracic Surg. **35**: 265, 1958.
4. Peddie, G. H., Creech, O., and Halpert, B.: Structural changes in the heart resulting from cardiac massage. Surgery **40**: 481, 1956.

Glynn, I. M.: The Action of Cardiac Glycosides on Sodium and Potassium Movements in Human Red Cells. J. Physiol. **136**: 148 (April 3), 1957.

Experiments were done on the fluxes of sodium and potassium across the human red cell membranes to determine whether the glycosides act on the transport mechanism by interfering with the energy mechanism during the "sodium pump" or by interfering with the carrier mechanism in the membrane of the cell. To test whether the action of the cardiac glycosides is one of interference with the transmission of energy to the "pump," experiments were done to study the fluxes in the presence and absence of glucose and with or without the inhibitor, digoxin. The potassium influx was related to the level of external potassium. This was measured by radioactive potassium uptake in red cells. With a fixed external potassium level a given dose of digoxin caused a given degree of inhibition of uptake of potassium. When glucose was removed from the experimental system, the effect of digoxin was unchanged. The efflux of labeled potassium from the cells was not influenced by the presence of glucose or digoxin. The efflux of sodium from cells on the other hand was greatly influenced when digoxin was added to the system. Sodium efflux was reduced by 50 per cent in this way, yet the efflux remained unaffected by glucose deprivation. The influx of labeled sodium was reduced 40 per cent when digoxin was added to the external environment, but the influx of labeled sodium was uninfluenced by the absence of glucose in the external environment.

The conclusions drawn from these experiments are that the action of cardiac glycosides cannot be explained by supposing that the drugs interfere with the energy supply to "pump"; their action must interfere with the mechanism by which ions penetrate the membrane. The author further studied the effect of substances of like chemical configuration to the cardiac glycosides on these fluxes. From these experiments it was possible to define certain molecular features that are necessary for such action on ion fluxes. This study shows that the cardiac glycoside competes with potassium ions for a site on the cell membrane where penetration of the ion occurs. From a study of these molecular movements, it is estimated that there are about 1,000 such sites on a red cell membrane.

Harvey

Traumatic Rupture of Interventricular Septum Proved by Cardiac Catheterization

By Scott R. Inkley, M.D., and Frank M. Barry, M.D.

A rare complication of trauma to the heart is rupture of the interventricular septum. The diagnosis of an acquired lesion of the septum can be reasonably made from history and cardiac catheterization and early recognition is of importance if immediate surgical correction is indicated.

RUPTURE of the interventricular septum due to trauma is a rare phenomenon, according to Pollock, Markelz and Shuey,[1] who reviewed all the reported cases up to 1952 and found a total of 12 proven traumatic interventricular defects. This report concerns a patient who developed an interventricular septal defect following severe trauma to the chest that was proven by cardiac catheterization.

Case Report

A 38-year-old white man was admitted to the University Hospitals of Cleveland after the milk delivery truck that he was driving was struck by another car. The patient had been crushed against the chest-high center platform of his truck by cases of milk falling from a shelf behind him. The blow was sudden and compressed the left chest anteroposteriorly.

On his admission, the pulse was 104, the respirations were 24 and the blood pressure was 104/68; he was in obvious respiratory distress from multiple rib fractures of the left chest. The right chest was clear to percussion and auscultation, and the left chest revealed hyperresonance to percussion, decreased breath sounds and tactile fremitus. Subcutaneous emphysema was present in the left axilla and neck. Except for multiple lacerations and abrasions of the face and extremities, no other serious injuries were noted.

The patient's early hospital course was marked by chest pain, dyspnea and cyanosis, but by the fifth day in the hospital there was marked improvement and on the eighteenth day the patient was discharged. Adequate auscultation of the left chest anteriorly was not possible, because of pain and a traumatic pneumothorax, until the patient returned to his surgeon in a follow-up visit at which time a loud systolic murmur was noted over the precordium. The heart was not enlarged to percussion, and a loud, blowing systolic murmur was heard best in the fourth interspace just to the left of the sternum. The murmur was transmitted to the cardiac apex and base.

A tentative diagnosis of traumatic interventricular septal defect was made, and the patient was admitted to the hospital for cardiac catheterization. The results of catheterization are seen in table 1; they show a pulmonary artery pressure at the upper limits of normal and definite evidence of a left-to-right shunt. This was considered confirmatory evidence of an interventricular septal defect. In establishing the development of the defect as secondary to the trauma sustained in the automobile accident, the results of 2 pre-employment physical examinations and of a selective service physical examination made prior to the accident were considered. In each instance, the heart was described as normal. It is improbable that a murmur of such intensity as the present one would be missed during even the most cursory examination. Following his discharge from the hospital the patient complained of some dyspnea on exertion, and chest pain associated with breathing. These symptoms gradually disappeared during the course of the next 6 months, and approximately 9 months after his injury he returned to work as a milkman in a rural community. His activity is somewhat restricted by fatigue, but he has done extremely well. He complains of no dyspnea with normal exertion. Electrocardiographic studies 18 months after the injury showed no significant change and a chest x-ray taken at the same time showed no evidence of cardiac enlargement. The auscultatory findings remained essentially unchanged during this period.

Discussion

Experimental studies on laboratory animals with the use of blunt force on the heart have

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TABLE 1.—*Cardiac Catheterization Studies*

Location	Pressure (mm. Hg)	Oxygen content (vol. %)	Cardiac output (L./min.)
Pulmonary artery	30/15 mean 24	13.0	
Right ventricle	30/0 mean 15	14.0	7.3
Right atrium	7/3	11.7	
Inferior vena cava		11.7	
Superior vena cava		11.6	
Femoral artery		16.1	
Left ventricle			4.4
Right-to-left shunt			2.9

Oxygen consumption 220 ml./min.

shown that rupture is most likely if the heart is struck late in diastole or early in systole.[2] The simple mechanics of rupture dictate that it would be most likely to occur when the ventricles are full and when the intraventricular pressure would rise highest with sudden compression of the ventricular walls. If the mitral and tricuspid valves are in the closed position, there is less chance for relief of pressure into the atria and the great veins. Presumably, the impact in this patient occurred when the ventricles were full, and the sudden elevation of pressure caused a rent in the septum that has been maintained by the normal pressure differential between the right and left ventricle. Other injuries that are likely with nonpenetrating trauma to the heart are rupture of the ventricular wall into the pericardial sac, fracture of mitral or tricuspid valves, or tearing of the chordae tendineae. Contusion of the ventricular muscle may also cause changes similar to myocardial infarction.[3] Electrocardiographic studies after injury may reveal evidence of muscle damage or pericardial irritation. In this instance electrocardiographic studies were not made during the acute stage of the illness. No significant limitation of physical activity has yet been necessary in this patient, and there has been no objective evidence of cardiac enlargement by x-ray or by electrocardiogram. Operative repair of the defect is contemplated, but the absence of symptoms, the relatively low pulmonary artery pressure and the normal electrocardiogram make it reasonable to postpone surgery for the present.

Traumatic rupture of the septum has been rarely reported but will be likely to appear more commonly as the result of more frequent use of the cardiac catheter. Since Pollock and co-workers[1] report of 12 cases in the literature in 1952, 1 case proven by cardiac catheterization,[4] 1 by autopsy[5] and 1 by surgical repair have been noted. Recognition of this defect is important because of the availability of surgical correction in those cases where a large shunt may be responsible for pulmonary vascular disease and cardiac failure.

SUMMARY

A case of traumatic rupture of the interventricular septum proved by cardiac catheterization is presented. The patient has returned to his occupation of milkman without symptoms or signs of cardiac embarrassment. Surgical repair of this defect will be considered in the future.

SUMMARIO IN INTERLINGUA

Es presentate un caso de ruptura traumatic del septo interventricular, demonstrate per catheterismo cardiac. Le patiente ha retornate a su occupation de lactero, sin symptomas o signos de embarasso cardiac. Le possibilitate de reparar le defecto per intervention chirurgic va esser considerate in le futuro.

REFERENCES

1. POLLOCK, B. E., MARKELZ, R. A., AND SHUEY, H. E.: Isolated traumatic rupture of interventricular septum due to blunt force. Am. Heart J. **43**: 273, 1952.
2. KISSANE, R. W.: Traumatic heart disease; non-penetrating injuries. Circulation **6**: 421, 1952.
3. MORITZ, A. R., AND ATKINS, J. P.: Cardiac contusion, an experimental and pathological study. Arch. Path. **25**: 445, 1938.
4. GUILFOIL, P. H., AND DOYLE, J. T.: Traumatic cardiac septal defect. Report of a case in which diagnosis is established by cardiac catheterization. J. Thoracic Surg. **25**: 510, 1953.
5. HALTER, B. L.: Non-penetrating trauma to the heart. Am. J. Surg. **90**: 237, 1955.

Cardiac Rupture due to Metastases from a Carcinoma of the Antrum

By Donald H. Singer, M.D., Bernard Czernobilsky, M.D., and Lester A. Steinberg, M.D.

ALTHOUGH neither cardiac rupture nor metastatic tumor to the heart is rare, their combination is exceedingly uncommon. This is a report of such an instance. This case also presents a third unusual feature, that of metastasis of "cancer to cancer."

Case Report

A 70-year-old White Russian Jewish man began to experience pain in the region of the right upper molar teeth late in March 1957. The first right upper molar tooth was removed shortly thereafter. The pain persisted, however, and the wound failed to heal properly. There was progressive swelling of the right upper jaw, as well as a foul-smelling sanguineous oozing from the site of extraction. Biopsy of the area revealed undifferentiated anaplastic carcinoma. He entered the Beth Israel Hospital on May 10, 1957.

The patient had had an episode of amebic hepatitis in 1939 and an acute myocardial infarction in October 1954.

Physical examination on admission revealed swelling of the right side of the face, a necrotic area in the right upper alveolus, and a firm right submandibular node of moderate size. The blood pressure was 120/70. Roentgenograms of the skull and paranasal sinuses (fig. 1) showed the right antral cavity almost totally obscured by an irregular soft-tissue mass extending into the adjacent nasal cavity. There was some destruction of the medial and lateral walls of the antrum as well as of the floor of the orbit. Chest and cervical spine, examined by x-ray, were within normal limits. An electrocardiogram revealed evidence of old anterolateral infarction (fig. 2, *left*). The hemoglobin level was 12.2 Gm. per cent, the hematocrit value was 37 per cent, and the white-cell count was 12,500 per ml. A urinalysis and blood nonprotein nitrogen determination were within normal limits. In preparation for a course of supervoltage x-ray therapy the right premolar and molar teeth were extracted, and an antral-oral fistula was created to facilitate drainage of the maxillary sinus.

Radiation therapy, in the amount of 6,000 r was administered on an outpatient basis during the succeeding 8 weeks, and initially gave considerable symptomatic relief. On July 16, however, the patient appeared chronically ill. He complained of pain and swelling of the right side of his face and of tiring easily. He had lost 25 pounds in 2 months. Three weeks later he was rehospitalized. The rectal temperature was 102° F. The right nasal cavity was almost obliterated by a friable, oozing, pink-grey mass. The right upper alveolus was necrotic and covered by a foul-smelling grey-green membrane. The heart and lungs were negative except for a grade II systolic murmur at the base. The abdomen was unremarkable. There was no peripheral edema. The hemoglobin level had fallen to 8.7 Gm. per cent, the white-cell count was 29,600 with 65 per cent neutrophils, and there was occult blood in the stool. Roentgenograms of the paranasal sinuses showed further destruction of the antral walls and floor of the right orbit. Three units of packed red blood cells were administered. The patient was discharged 2 days later, on August 11, feeling much improved and with a hemoglobin of 11.8 Gm. per cent.

Inability to retain solid food and increasing pain necessitated rehospitalization 2 days later. The hemoglobin level was unchanged, the white cell count had risen to 34,400, with 91 per cent neutrophils, and the urine was unremarkable.

On the afternoon of August 14 the patient vomited and suffered acute vascular collapse. There was no pain. An electrocardiogram revealed sinus tachycardia and nonspecific S-T and T changes (fig. 2, *right*). The hemoglobin level was essentially the same. An infusion of levarterenol was begun. Three hours later the neck veins appeared distended. The heart was enlarged to the left and right, and the heart sounds were more distant. The liver was felt 3 cm. below the right costal margin. The lungs remained clear. A repeat electrocardiogram was unchanged. A portable chest x-ray (fig. 3) showed cardiomegaly and increased bronchovascular markings. Rapid digitalization was begun. The patient's condition deteri-

From the Departments of Medicine and Pathology, Beth Israel Hospital, Boston, Mass.

FIG. 1. Roentgenogram of skull and paranasal sinuses showing right antrum occupied by soft-tissue mass, with invasion of adjacent nasal cavity.

iorated during the night. The next morning he was semistuporous. The peripheral signs of right-heart failure had increased, and the heart sounds were barely audible. He complained of mild precordial pain. Shortly thereafter he became comatose and died. Just prior to death, an electrocardiogram again failed to reveal significant changes, a white count was 84,000, and a serum glutamic oxaloacetic transaminase level was 537 units.

PATHOLOGY

At autopsy the right maxillary antrum was occupied by a necrotic, grey mass that extended through the antral wall into the right nasal cavity, and from there into the vestibule of the oral cavity. The pericardial sac was large and bulging, and contained 500 ml. of liquid blood. The heart weighed 380 Gm. A reddish, grey mass, measuring 3.5 by 3.0 by 0.6 cm., was present on the anterior aspect of the right ventricle, near the base. The center of the mass was necrotic, and communicated with the lumen of the right ventricle (fig. 4). Two similar masses were situated at the base of the left ventricle and on the posterior wall of the right atrium, but no perforations were noted in these areas. A 1.5 by 1.0 by 1.0 cm. mass protruded from the myocardium into the cavity of the right ventricle, beneath the chordae tendineae of the tricuspid valve. Yellow-red tumor nodules, 0.5 to 1.0 cm. in diameter, were also found in both lungs, the liver, and in the submucosa of the small in-

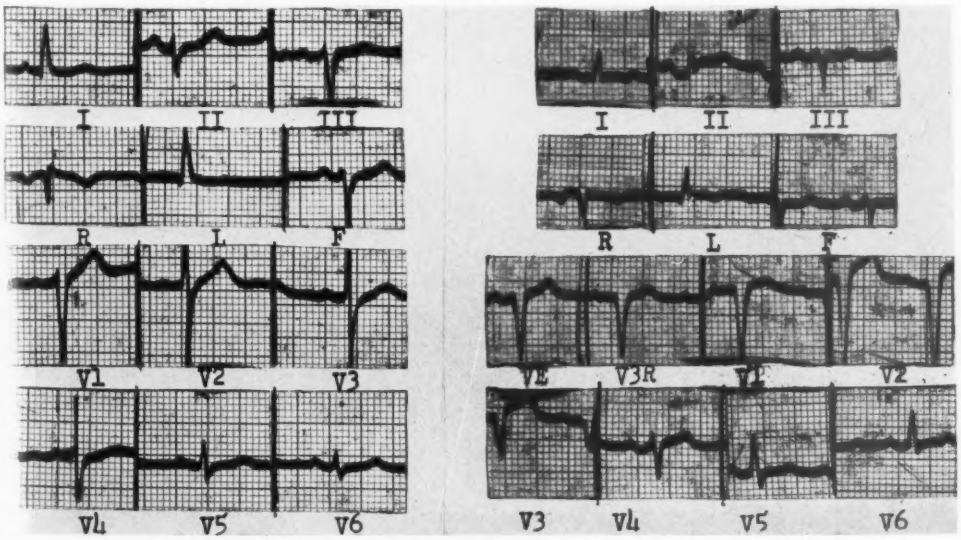

FIG. 2. Electrocardiograms. *Left.* May 11, 1957. Residual changes of old anterior myocardial infarction. *Right.* August 14, 1957. Sinus tachycardia with nonspecific S-T and T changes.

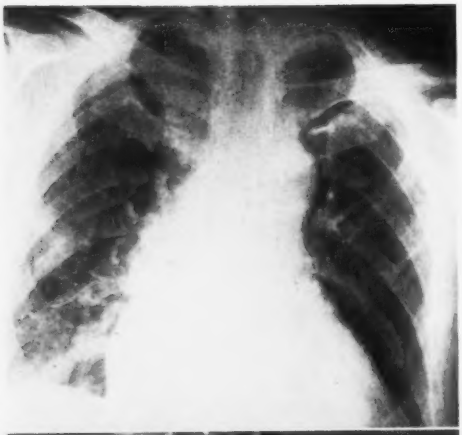

FIG. 3 *Top.* Portable chest roentgenogram showing moderate cardiomegaly and increased bronchovascular markings.

FIG. 4 *Bottom.* Tumor mass at the base of the right ventricle with arrow pointing to central perforation.

testine. A similar yellow nodule in the cortex of the left kidney proved to be a clear-cell renal adenoma rather than a metastatic mass.

The peritoneal cavity contained 1,000 ml. of clear, amber fluid. The liver weighed 2210 Gm., and was congested. The single, firm right submandibular node was not examined.

On microscopic examination the antral mass was composed of bizarre cells, with very large and irregular nuclei and nucleoli. The chromatin pattern was reticulated. Numerous mitotic figures, some atypical, were noted. Giant tumor cells were also present. The cells had a spindle-shaped appearance and tended to be loosely arranged in sheets. The histological appearance was that of a highly anaplastic carcinoma. The metastatic nodules, including those in the heart, were made up of cells identical with those seen in the primary antral tumor (fig. 5). Within the clear-cell adenoma of the left kidney could be seen groups of metastatic tumor cells from the antrum (fig. 6).

DISCUSSION

Tumor metastases to the heart and pericardium are no longer considered rare entities. The incidence of cardiac spread in patients suffering from malignant disease, exclusive of lymphomas and leukemias, has ranged in more recent series to as high as 10.9 to 19.1 per cent.[1–6] Series including leukemias and lymphomas have shown an even higher incidence.[2–4] Although carcinomas of almost every organ system have been described as giving rise to cardiac metastases, those arising in the bronchus and the breast account for the bulk of recorded cases.[1–8] Carcinoma of the antrum, on the other hand, rarely spreads to the heart. Only one other recorded instance was found.[8]

Despite the frequency of cardiac metastases, resultant rupture of the heart is exceedingly rare. A survey of the literature yielded only 3 documented cases. Krumbhaar and Crowel, in their 1925 review,[9] mentioned a case of rupture of a heart invaded by melanotic sarcoma, but gave no details. Costa, in 1931,[10] described left atrial rupture secondary to leukemic infiltration of the heart. More recently McNamara et al.[11] recorded a similar instance associated with carcinoma of the duodenum.

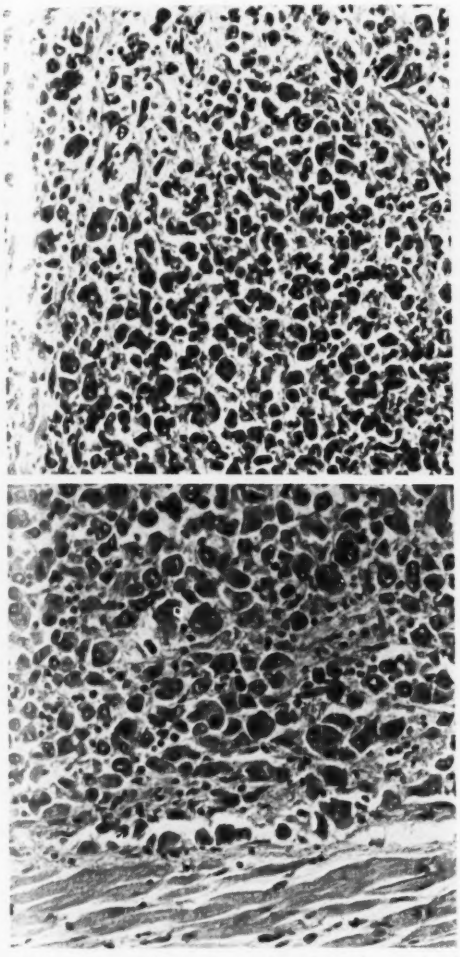

FIG. 5. *Top.* Histologic section through anaplastic carcinoma of maxillary sinus. × 170. *Bottom.* Section through right ventricle showing tumor metastasis of cells identical to those in the antrum, adjacent to a segment of uninvolved myocardium.

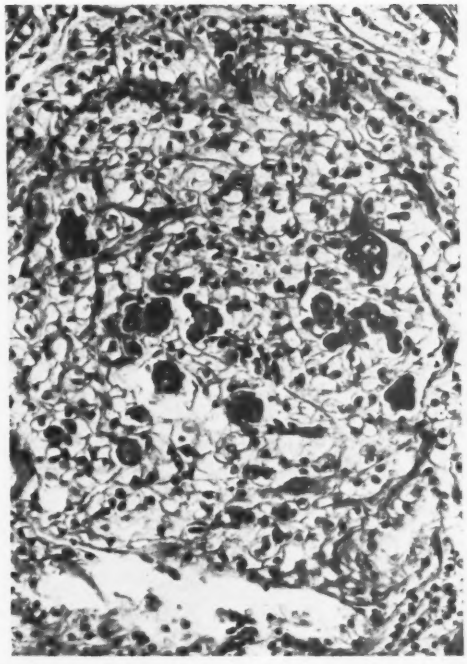

FIG. 6. Metastatic cells from antral carcinoma scattered among cells of a clear-cell adenoma of left kidney. × 170.

The present case represents a fourth instance of rupture as a sequel to cardiac metastases.

An antemortem diagnosis of tumor invasion of the heart was not made. In the light of the patient's known coronary heart disease, including at least 1 acute myocardial infarction, it seemed entirely probable that the terminal episode was due to another infarct. Pulmonary embolism and dissecting aneurysm were also briefly considered. The possibility of neoplastic infiltration of the heart was not even entertained. This difficulty in antemortem diagnosis is in conformity with the general experience. Doane and Pressman in 1942[12] were able to find only 20 documented cases in which such a diagnosis had been made. Brick and Greenfield[13] contributed 2 more cases in 1947. Since that time several other cases have been reported, but the total number remains small. The infrequency with which a clinical diagnosis of this condition is made stems, of course, from the failure of cardiac tumors to produce specific signs and symptoms. They are either silent, as is usually the case, or they may present any of the whole gamut of cardiovascular symptoms including congestive failure, arrhythmias, atrioventricular block, chest pain, vena caval obstruction, or cardiac tamponade. Roentgenograms and electrocardiograms have usually been of little specific diagnostic significance, as in the present case. The major point in antemortem diagnosis

must therefore continue to be a high index of suspicion in patients with known malignant disease who develop new, increased, or intractable symptoms of cardiac disease.[1, 12-13] Rarely, such a clinical evaluation may be of more than strictly academic interest, as illustrated by reports of reversal, by x-ray therapy, of atrioventricular block secondary to leukemic infiltration of the interventricular septum.[14-15]

An additional point of interest in this case is the occurrence of a metastasis from the antral carcinoma into a clear-cell adenoma of the left kidney. Metastasis of "cancer to cancer" is a rare phenomenon. Rabson et al.[16] were able to verify only 19 such instances up to 1954. The case here reported represents the second instance of such metastasis in the recent autopsy material at the Beth Israel Hospital. A previous case also involved the spread to a renal-cell carcinoma (hypernephroma), but from a primary carcinoma of the bronchus. It is of interest that carcinomas of the kidney have been the seat of the metastatic lesions in two thirds of Rabson's cases, as well as in both those presented here.

Summary

The case is described of a 70-year-old white man with a primary anaplastic carcinoma of the right maxillary antrum, and with widespread visceral dissemination, including metastases to the heart. Myocardial rupture was noted to have occurred through one of the metastatic lesions. To the best of our knowledge this is the fourth instance of rupture as a sequel to tumorous infiltration of the heart.

Among the metastases were one or more to a clear-cell adenoma of the left kidney. This instance of metastasis of "cancer to cancer" is the second case of this rare condition in the recent autopsy material of the Beth Israel Hospital.

Acknowledgment

The authors wish to express their appreciation to Dr. David G. Freiman, pathologist in chief, and to Dr. Felix Fleischner, radiologist in chief of the Beth Israel Hospital for their constructive advice and assistance in the preparation of this report.

Summario in Interlingua

Es describite le caso de un masculo de ra ia blanc de 70 annos de etate con carcinoma a aplastic primari del antro dextero-maxillar e extense dissemination visceral, incluse met stases al corde. Esseva notate que rupt a myocardial habeva occurrite a transverso n del lesiones metastatic. Secundo nostre inf rmationes, isto es le quarte reporto de rupt a como sequella a infiltration tumorose el corde.

Le metastases includeva un o plures a n adenoma a cellulas clar del ren sinistre. Co o caso del rar condition de metastase de "cancere a cancere," isto es le secunde incontr te in recente materiales necroptic del Hospi al Beth Israel.

References

1. Scott, R. W., and Garvin, C. F.: Tumors of the heart and pericardium. Am. Heart J. **17**: 431, 1939.
2. Gould, S. E.: Pathology of the Heart. Springfield, Ill., Charles C Thomas, Publisher, 1953.
3. Bisel, H. F., Wroblenski, F., and LaDue, S. S.: Incidence and clinical manifestations of cardiac metastases. J.A.M.A. **153**: 712, 1953.
4. Burnett, R. C., and Shimken, M. B.: Secondary neoplasms of the heart. Arch. Int. Med. **93**: 205, 1953.
5. DeLoach, J. F., and Haynes, J. W.: Secondary tumors of the heart and pericardium. Arch. Int. Med. **91**: 224, 1953.
6. Young, J. M., and Goldman, I. R.: Tumor metastases to the heart. Circulation **9**: 220, 1954.
7. Landing, B. H., and Farber, S.: Tumors of the Cardiovascular System. Washington, D.C., Armed Forces Institute of Pathology, 1956.
8. Prichard, R.: Tumors of the heart. Review of the subject and report of 150 cases. Arch. Path. **51**: 98, 1951.
9. Krumbhaar, E. B., and Crowell, C.: Spontaneous rupture of the heart. Am. J. M. Sc. **170**: 828, 1925.
10. Costa, A.: Rara forma do rottura dell 'at ia sinistra del cuore per infiltrati leucemici el miocardia. Sperimentali Arch. di Biol. 5: 117, 1931.
11. McNamara, W. L., Ducey, E. F., and Bak r, L. A.: Cardiac rupture associated v th metastases to the heart from carcinoma of

the duodenum. Am. Heart J. **13**: 108, 1937.

12. Doane, J. C., and Pressman, R.: Antemortem diagnosis of tumors of the heart. Am. J. M. Sc. **203**: 520, 1942.
13. Brick, I. B., and Greenfield, M.: Reticulum cell sarcoma with cardiac metastases. Report of 2 cases with antemortem diagnosis in one. Am. Heart J. **34**: 599, 1947.
14. Shelburne, S. A., and Aronson, H. S.: Tumors of the heart. Report of a secondary tumor of heart involving pericardium and bundle of His with remission following deep roentgen ray therapy. Ann. Int. Med. **14**: 728, 1940.
15. Blotner, H., and Sosman, M. C.: X-ray therapy of the heart in a patient with leukemia. New England J. Med. **220**: 793, 1944.
16. Rabson, S. M., Stier, P. L., Baumgartner, J. C., and Rosenbaum, D.: Metastasis of cancer to cancer. Am. J. Clin. Path. **24**: 572, 1954.

Rimsa, A., and Griffith, G. C.: Trends in Cardiovascular Syphilis. Ann. Int. Med. 46: 915 (May), 1957.

At the Los Angeles County Hospital, the charts of 954 patients with known cardiovascular syphilis were analyzed to determine trends in incidence, diagnosis, treatment, and prognosis during the years 1945 to 1954. In that period, the incidence of cardiovascular syphilis decreased approximately 47 per cent. Twenty-six and eight tenths per cent of the patients were found to have syphilitic aortitis; 49.5 per cent, syphilitic aortic insufficiency; 9.3 per cent, syphilitic aortic insufficiency associated with syphilitic aortic aneurysm; 14.0 per cent, syphilitic aortic aneurysm. The most common complication was congestive failure. Less frequent complications were hypertension and angina pectoris. The latter 2 developments definitely made the prognosis less favorable. Blood serologic reactions for syphilis were positive or repeatedly doubtful in 82 per cent of all patients studied. Radiologic findings were normal in only 8.8 per cent of 633 patients examined. Normal electrocardiograms were obtained in less than 4 per cent of patients examined. No electrocardiographic pattern pathognomonic of cardiovascular syphilis was noted. In the abnormal electrocardiographic records, the changes were diagnostic of either atrioventricular conduction defect, intraventricular conduction defect, or left ventricular hypertrophy. Penicillin was confirmed as the drug of choice for the treatment of cardiovascular syphilis. Progression of cardiovascular lesions was halted and untoward reactions were less frequent than were reactions following adequate treatment with bismuth or arsenic compounds. Prognosis as to long-term survival was best in the younger age groups because penicillin therapy was available to them. Nevertheless, at least 85 per cent of the patients in this study died from the sequelae of syphilitic cardiovascular lesions in the first 5 years after cardiovascular syphilis was diagnosed. The average age at the time of death for all patients was 62.3 years. The principal cause of death was congestive heart failure. However, among the patients with aortic aneurysm, rupture of the aneurysm was the main cause of death and in the patients in whom hypertension developed in conjunction with syphilitic aortic aneurysm, death was generally the result of a dissecting aneurysm developing at the site of the syphilitic aneurysm.

Wendkos

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Syndrome of Carotid Artery Insufficiency

Early Clinical Recognition and Therapy

By LAMAR E. CREVASSE, M.D., R. BRUCE LOGUE, M.D., AND J. WILLIS HURST, M.D.

DR. LOGUE: Carotid artery insufficiency is a relatively common but frequently unrecognized syndrome. Fisher[1] in 432 consecutive autopsies in which the brain and carotid arteries were studied found 28 cases of complete occlusion of one or both carotid arteries. Thirteen cases showed very severe narrowing of the arterial lumina, making a total of 9.5 per cent with advanced carotid disease. The classic concept of carotid artery thrombosis, namely monocular blindness and contralateral hemiplegia, is the exception rather than the rule, since visual disturbances occur in only 15 per cent. Furthermore, about 15 per cent of patients with carotid artery thrombosis may have no symptoms.[1] Like atherosclerotic occlusions in other vessels, occlusion of the internal carotid artery is more common in the male over 40, although the age group varies from 13 to 85 years. Occlusions in the younger age group are not infrequent. Any disease process producing occlusive vascular disease may be implicated. By far the most frequent offender is atherosclerosis with a normal blood pressure. Hypertensive persons for some unknown reason are less frequently affected by this syndrome. Angiitis of any cause, trauma, embolus, compression of the internal carotid by the lateral process of the atlas,[2] and rarely syphilis have been implicated.

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The arterial blood supply to the head is illustrated in figure 1. The internal carotid artery bifurcates from the common carotid artery distal to the carotid bulb and courses through the retropharyngeal space into the cranium, giving off as its first branch the ophthalmic artery. The central retinal artery branches from the ophthalmic coursing through the optic nerve furnishing the blood supply to the retina. It is an end artery with no collateral circulation. Other branches of the ophthalmic, however, have rich collateral circulation, with both the ipsilateral external carotid and contralateral internal and external carotids. The internal carotid artery subsequently branches into the posterior communicating, anterior choroidal, anterior and middle cerebral, thus providing the blood supply for the homolateral retina, frontal, temporal, parietal lobes and posterior limb of the internal capsule. The clinical pattern of the syndrome and specific symptoms are determined by the adequacy of the collateral circulation. Approximately 15 per cent of the patients with complete carotid occlusion may have no neurologic symptoms because of adequate collateral circulation.

In the past, the finding of thrombosis of the internal carotid artery has commonly been attributed to retrograde extension from the middle cerebral artery, rather than originating from the cervical portion of the carotid artery. Routine autopsy examinations of the cervical portion of the internal carotid is seldom done. It is well to note that in Fis-

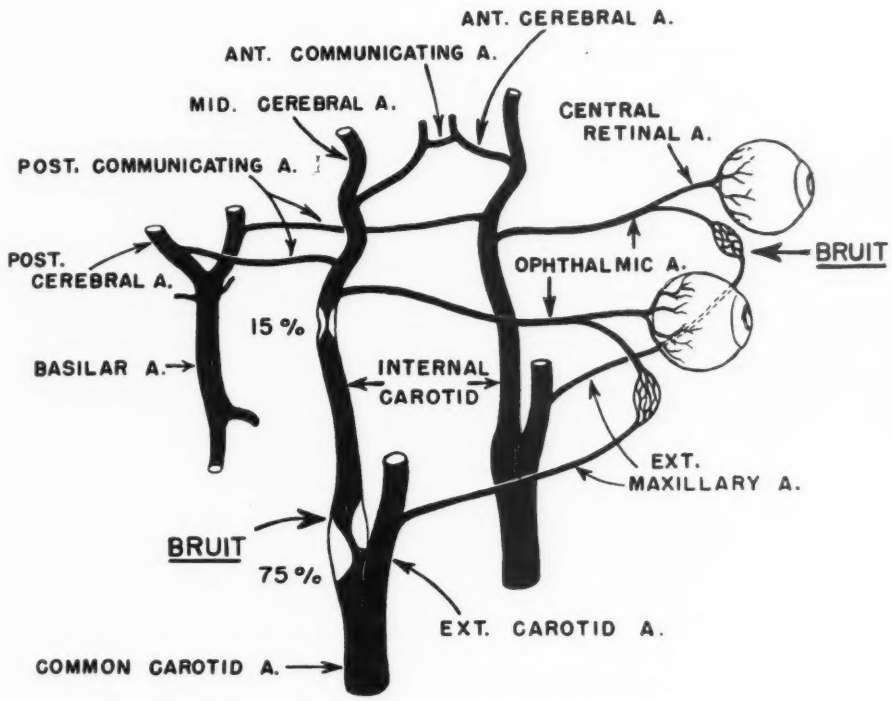

FIG. 1. The major cerebral arterial blood supply and its collateral circulation are schematically illustrated. The approximate percentages and sites of carotid obstruction are indicated. The common sites of arterial bruits associated with carotid insufficiency are labeled.

er's analysis, thrombotic occlusion of major vessels adjacent to the circle of Willis was seen only 12 times in a total of 218 cases with vascular lesions. In striking contrast, carotid occlusion or severe stenosis was present in 41 cases, approximately the same frequency as cerebral hemorrhage and hypertensive atherosclerotic encephalomalacia. Necropsy examination of patients with "cerebral thrombosis" in the past has frequently shown confusing pathologic findings. Areas of extensive softening or infarction have been noted without anatomic obstruction of the cerebral vessels. It is becoming quite clear that with complete examination of the brain and carotids that carotid artery thrombosis and stenosis is a commonly overlooked etiologic factor.

It is apparent that the problem of carotid disease, its incidence, and the spectrum of clinical findings associated with carotid artery disease is today poorly formulated. The following cases are representative of this broad spectrum.

Case 1

M.P., a 55-year-old white woman, experienced 4 transient episodes of monocular blindness 15 months prior to admission. Three involved the right eye and 1 the left eye, and the attacks were always associated with the upright position. The episodes consisted of a sensation of a window shade descending gradually over the eye until total monocular blindness occurred. After approximately 1 minute the vision would return rather jerkily by levels until there was complete restoration of vision. There were no associated motor or sensory disturbances. The patient remained symptom free until 3½ months prior to admission, when she noted progressive difficulty in the use of the right hand. Two months prior to admission there was a transient episode of left-sided weakness. There was no history of diplopia, vertigo,

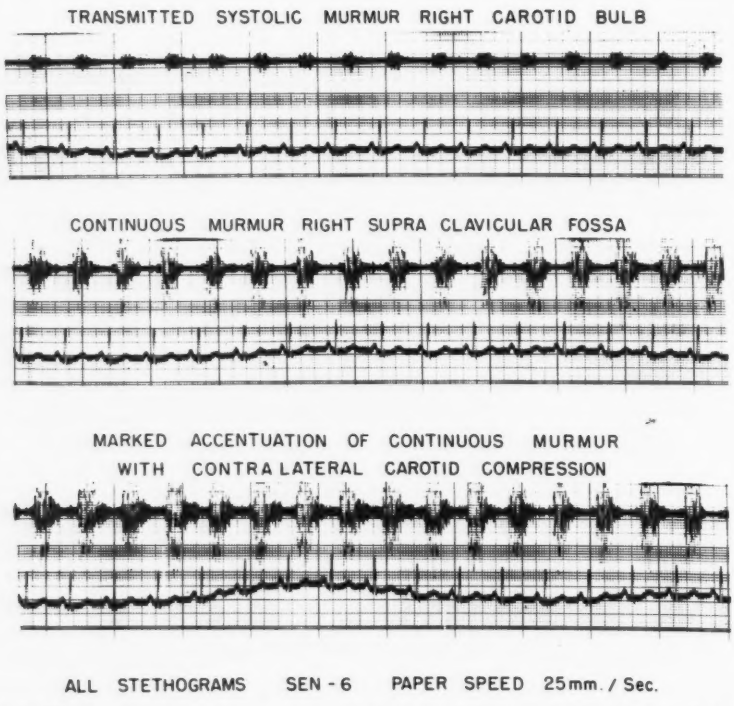

FIG. 2. Well-localized continuous murmur at the base of the neck in the right supraclavicular fossa in the aortic arch syndrome. A faint systolic murmur is transmitted up the right carotid only. The marked accentuation of the continuous murmur on contralateral carotid compression is related to an increase in systolic and diastolic pressure gradients across the partially obstructed right innominate by a further reduction in collateral blood flow.

or dysphasia. Her father died of a cerebral vascular accident at age 73 and a sister died of coronary thrombosis at age 43. The blood pressure was 140/90 mm. Hg in the left arm and 110/90 mm. Hg in the right. The right radial pulse was diminished. The carotid vessels pulsated vigorously to the angle of the jaw. Auscultation over the right carotid revealed a harsh grade III systolic murmur. There was a palpable thrill over the left carotid bulb, and a grade III continuous murmur was present. Changes in position, jugular compression, and the Valsalva maneuver produced no appreciable changes in the murmurs. There was no evidence of venous collaterals. Carotid compression just proximal to the bulb obliterated the murmur on the ipsilateral side and accentuated the contralateral murmur. On compression of the left carotid artery the previously noted systolic murmur over the right carotid bulb became continuous. There was bilateral diminution of the pharyngeal carotid pulsations and this was more evident on the left. The visual fields were normal. The fundi revealed grade II changes. The heart was not enlarged and there was a grade I to II aortic systolic murmur. The neurologic examination was negative except for motor weakness of the right arm. The cranial nerves were intact, save for slight flattening of the left nasolabial fold. The remainder of the neurologic examination was normal. The electrocardiogram was normal. X-rays of the skull and neck revealed calcium plaques in the carotid arteries. The serum cholesterol was 299 mg. per cent. The electroencephalogram was normal. Following compression of alternate carotids for 10 seconds frontal dysrhythmic changes occurred on the side of carotid compression.

The patient experienced one episode of left-sided weakness concomitant with a drop in blood pressure from 140/90 to 120/80, probably induced by oversedation. Function rapidly returned with restoration of blood pressure to the previous level. The patient's condition has remained stable on short-term anticoagulant therapy.

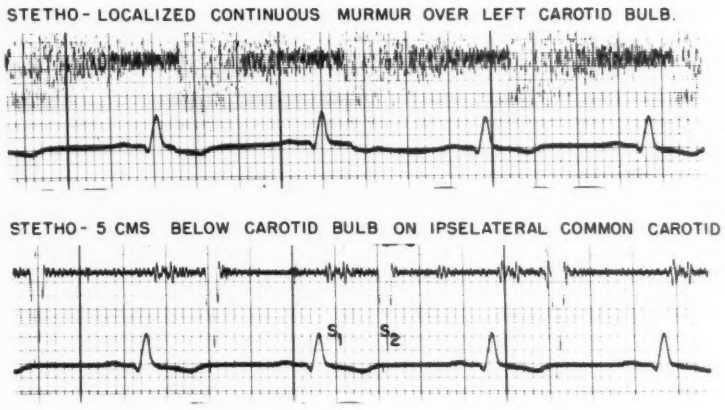

FIG. 3. Well-localized continuous murmur over left carotid bulb in carotid artery insufficiency. In contrast to figure 2 the murmur is rarely present at the base of the neck or lower on the common carotid.

DR. CREVASSE: The history and physical findings are quite typical of bilateral carotid artery insufficiency. Premonitory signs and symptoms such as transient, localized motor and sensory disturbances, hemiparesis, monoparesis, and visual difficulties may be observed from days to years before a permanent vascular accident occurs in the majority of patients. This patient illustrates the long duration of premonitory symptoms eventuating in a progressive neurologic picture simulating brain tumor. This pattern occurs in 15 to 25 per cent of reported patients. Early recognition of this group with premonitory symptoms is paramount in regard to therapy.

A PHYSICIAN: How can this be differentiated from the aortic arch syndrome or "reversed coarctation"?

DR. CREVASSE: The clinical features and symptoms of these 2 syndromes may closely overlap. Briefly the aortic arch syndrome occurs in the younger age group, is usually associated with muscle group ischemia and atrophy of the muscles supplied by the great vessels arising from the arch.

The asymmetry or absence of blood pressure in the upper extremities is well known, but blood pressure variation or absence of a radial pulse not infrequently occurs simultaneously with carotid artery thrombosis alone and represents segmental obstructions. In the aortic arch syndrome the carotid pulsations are usually diminished at the base of the neck and all the reported bruits have been maximal at this site (fig. 2). By contrast in carotid artery insufficiency, an occlusion may be detected high in the neck or the pulsations may be vigorous to the angle of the jaw and diminished or absent in the pharynx. The bruits are maximal over the carotid bulb (fig. 3).

Case 2

J.P., a 75-year-old white man, suddenly developed paralysis of the right arm and leg and inability to speak. The blood pressure was 130/80 bilaterally. There were aphasia and right hemiplegia. The left carotid pulsations terminated abruptly at the carotid bulb. The right carotid pulsated vigorously to the angle of the jaw. Palpation of the pharyngeal segments of the internal carotid revealed good pulsations on the right and none on the left. Auscultation of the right carotid bulb revealed a faint systolic bruit. The heart was normal.

DR. CREVASSE: About one half of the cases of carotid artery thrombosis simulate the

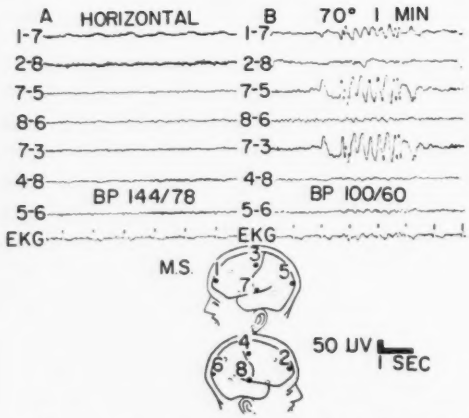

FIG. 4. Electroencephalogram of a 75-year-old woman with myxedema, postural syncope, and occlusion of the left carotid artery. Note the burst of high-voltage delta activity appearing primarily in the left temporal region after lowering of blood pressure by postural tilt. *(Reproduced from Neurology 6:464, 1956, by permission of the authors and the publishers.)*

routine stroke. Aphasia is present in approximately 50 per cent of cases and may be quite prominent, even though the carotid thrombosis may be on the side opposite the dominant hemisphere.

A PHYSICIAN: How can carotid occlusion be differentiated from the routine middle cerebral artery thrombosis?

DR. CREVASSE: Preceding episodes of transient motor weakness or sensory symptoms occurring primarily in the upright position or after maneuvers that provoke hypotension, postural or otherwise, are quite typical of impending carotid thrombosis.

By angiographic studies[3] about 75 per cent of the complete or partial occlusions are just above the bifurcation of the common carotid and 15 per cent at the siphon, with the remaining 10 per cent in varied locations (fig. 1). This produces several interesting physical findings that are most useful in the clinical diagnosis. It is well to remember, however, that physical findings including neurologic deficits may be absent, particularly in the premonitory phases.

Palpation of the neck at the angle of the jaw may reveal a diminished or absent pulsation. Occasionally a thrill is felt over the partially occluded vessel. More important, however, is the gentle palpation of the lateral portion of the pharynx using a wet glove. Absence or diminution of pulsation of the pharyngeal segment of the internal carotid is a consistent and reliable physical finding.[4] Thus, when an occlusion is suspected and the carotid pulse is absent in the neck or on pharyngeal palpation, the diagnosis would appear unequivocal. Since approximately 15 per cent of people with occlusion of the carotid artery will have no neurologic symptoms, cases of expanding intracranial lesions may co-exist with asymptomatic carotid artery occlusion.

The finding of a pulse in clinically suspected cases should not deter one from the diagnosis but indicates the need for further study by laboratory methods. Bruits over the eyeball[5] and carotids[6] in conjunction with palpation are quite helpful in that they are unlikely to occur with small-vessel occlusions above the circle of Willis.

A PHYSICIAN: How do you explain the presence of good pulsations in the neck and pharynx in some cases of carotid thrombosis?

DR. CREVASSE: The explanation for a palpable pharyngeal pulse in proved cases of occlusion are threefold. Since the occlusion is at the carotid siphon in approximately 15 per cent of cases (fig. 1), pulsations in the neck and pharynx, of course, will be normal. Secondly, a palpable pharyngeal pulse may represent transmitted pulsations from the more laterally positioned external carotid artery. Lastly, spasmodic contractions from the stimulated pharyngeal musculature may simulate arterial pulsations. For these reasons, the finding of a normal carotid pulse in the neck or pharynx only makes the diagnosis more elusive, but certainly not untenable.

Case 3

J.S., a 59-year-old white diabetic man, developed episodes of numbness and weakness in the right arm and leg associated with a stumbling gait 6 months prior to admission. On one occasion there was transient aphasia. These episodes occurred primarily in the upright position whi

w king, lasted 4 to 5 minutes, and promptly cl red with rest. After being given a Rauwolfia p paration because of mild hypertension, the p ent noted a marked increase in number of th e episodes. He discontinued his medication a there was an abrupt decline from 10 to 15 t pproximately 1 such episode each day. The b d pressure was 190/90. The fundi showed g de II changes. The right posterior tibial p se was absent. The left carotid pulsations w e absent below the angle of the jaw. The r ht carotid pulsated vigorously. The pharyngeal s ments were not palpable. There were no bruits o r the head or carotids. The neurologic examination was normal. The electrocardiogram revealed left ventricular hypertrophy. The serum cholesterol was 360 mg. per cent. Anticoagulant therapy was instituted and there was no recurrence of symptoms during a short follow-up period.

DR. CREVASSE: This case demonstrates a phenomenon that may occur in patients with cerebral vascular disease treated with hypotensive agents. The pathophysiology of these symptoms now seems clearer. In general, 55 to 60 mm. Hg is the critical systolic blood pressure to maintain adequate cerebral circulation, but with a compromised cerebral vascular circulation the critical blood pressure is considerably higher, and seemingly insignificant falls in blood pressure may cause significant symptoms. Shanbrom and Levy[7] observed the appearance of hemiplegia in a case of carotid thrombosis when the blood pressure fell below 160 mm. Hg following carotid arteriography. When the blood pressure was maintained above this level by vasopressor agents, the hemiplegia would resolve, only to reappear when the pressure fell again below this level. We have recently observed a patient with basilar artery insufficiency with tetraplegia precipitated by a fall in blood pressure from 200/110 to 130/110 incident to myocardial infarction. Restoration of function on 1 side with clearing of the sensorium rapidly occurred when the blood pressure was again maintained with vasopressor agents at 200 mm. systolic.

Meyer et al.[8] studied a group of 36 patients with recurrent signs and symptoms of major arterial insufficiency to the head in the light of the electroencephalogram, electrocardiogram, and clinical manifestations as the

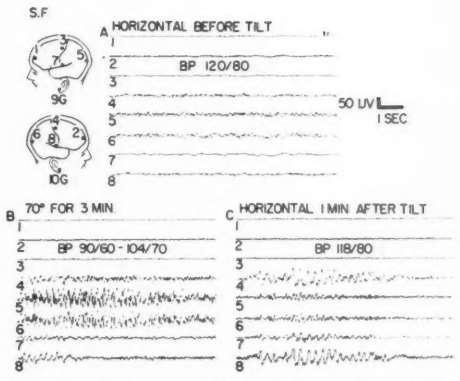

FIG. 5. Electroencephalogram of a 78-year-old man with basilar artery insufficiency before and after postural tilt. *(Reproduced from Neurology 6:464, 1956, by permission of the authors and the publishers.)*

blood pressure was lowered by repeated postural tilting on the tilt table and by carotid artery compression. When hypotension was produced on the tilt table or more commonly following carotid compression, neurologic symptoms could often be reproduced. Striking abnormalities of the electroencephalogram occurred during hypotension or carotid compression, whereas changes were not reproducible in normal subjects, patients with surgican ligation of the carotid artery, or elderly subjects with normal cerebral vascular function. Patients with carotid or basilar obstruction developed cerebral dysrhythmias over the regions supplied by the respective vessels when seemingly insignificant falls in blood pressure were produced on the tilt table (figs. 4 and 5).

Carotid artery insufficiency or thrombosis is usually present when transient or persistent hemiplegia occurs in relation to shock. Total or partial blockage of 1 carotid can exist without symptoms and be unmasked during a period of abnormal lowering of the blood pressure. Patients with a combination of cerebral vascular and cardiac disease are prone to episodes of postural ischemia to the brain, since postural fall in blood pressure is much greater in these patients.[8]

Postural hypotensive maneuvers and agents such as Rauwolfia, chloropromazine, and ganglionic-blocking agents are closely analo-

gous to the tilt-table observations and should be avoided in all patients with cerebral vascular insufficiency. Furthermore, one should correct promptly in these patients hypotension incident to cardiac arrhythmia, myocardial infarction, blood loss, acute left ventricular failure, anesthesia, or other less common etiologies.

A PHYSICIAN: What is the role of cerebral angiospasm in the production of symptoms?

DR. CREVASSE: From clinical observations in man and laboratory evidence in animals where the cerebral vessels can be viewed through a skull window, alterations in blood flow related to changes in systemic arterial pressure rather than cerebral angiospasm seem to be the major factor. It is difficult, however, to explain the transient neurologic deficits accompanying migraine headaches and, of course, arteriospasm has been observed by neurosurgeons operating on the circle of Willis.

A PHYSICIAN: Can carotid artery thrombosis be established without resorting to arteriography?

DR. CREVASSE: Carotid artery insufficiency and thrombosis is rapidly becoming a clinical diagnosis. Ophthalmodynamometry is a valuable adjunct in the diagnosis and consists of insertion of a gage with a spring-loaded plunger between the lid and sclerae for the measurement of intra-ocular pressure. The retinal arteries are observed with the ophthalmoscope as pressure is gently increased. When the retinal arteries begin to pulsate this represents the diastolic pressure and can be interpreted from the gage. The intraocular pressure is further increased until pulsations cease, and this reflects systolic pressure. This is repeated in the opposite eye. There is a striking pressure differential between the involved and the opposite eye, a reflection of carotid arterial obstruction. The average retinal artery pressure has been found to be 30 to 45 mm. Hg diastolic and 65 to 75 mm. systolic, that is, approximately half the systemic blood pressure.[9] It seems that a reduction of 25 to 30 per cent in both systolic and diastolic pressures is diagnostic of impaired carotid circulation.[10]

Case 4

J.A., a 47-year-old white man, developed episodes of sudden blindness in the right eye, characterized by a fog rolling in from the temporal side until vision was completely obscured. The blindness lasted 4 to 5 minutes and vision returned gradually from the nasal to the temporal side. During the past year he has had repeated episodes of weakness and numbness of the left arm and leg, not accompanied by visual symptoms. There have been persistent and severe frontal headaches for the past 8 months. Mental acuity has progressively diminished.

The blood pressure was 160/90. There was slight aphasia with moderate weakness of the left arm and leg. There was a systolic bruit over the left eye ball. The fundi were normal. The right pharyngeal pulse was absent. The reflexes were hyperactive on the left. The right carotid pulsation ended abruptly at the bulb, and the left pulsated vigorously. A grade II systolic murmur was present over the left carotid bulb.

A right carotid arteriogram demonstrated occlusion below the right carotid bulb. A thromboendarterectomy was performed by Dr. Garland Perdue but despite removal of the thrombus and passage of a catheter into the carotid siphon no back flow from the distal carotid occurred. The immediate postoperative course was characterized by recurrent episodes of monocular blindness at which time his blood pressure was 10 to 20 mm. Hg lower than when he was asymptomatic.

DR. CREVASSE: Monocular blindness and contralateral neurologic deficits are the hallmark of carotid artery thrombosis. As in this case, they usually do not occur simultaneously. This patient has severe headache, which is present in about half of all reported cases. The combination of headache, changes in mental acuity, neurologic deficits, and seizures frequently occurs in carotid artery thrombosis and is invariably confused with brain tumor.

The systolic bruits over the eyeball and carotid bulb opposite the occluded carotid are valuable signs in diagnosis and probably represent a compensatory increase in blood flow through the opposite partially involved carotid artery.

A PHYSICIAN: What is the significance and mechanism of monocular blindness?

DR. CREVASSE: Monocular blindness is usually transient lasting from 2 to 3 minutes and is subjectively described as a fog rolling

a veil coming over the eye, or a curtain dually obscuring vision. This type of ndness is typical of retinal ischemia. Since central retinal artery is an end artery g. 1) with no collateral circulation, alter- ions in blood flow through this vessel on the ie of a partially or completely occluded rotid is markedly affected by spontaneous lls in blood pressure or cardiac output. We ve made observations on the preceding pa- nt, and indeed when monocular blindness curred his systolic blood pressure was 10 20 mm. Hg lower than when he was asymp- matic. With falls in blood pressure, the ndus became pale, with a decrease in cali- er of the branches of the central retinal rtery, and retinal ischemia and blindness followed. When the factors that have re- duced blood flow were compensated or cor- rected, vision returned.

Paradoxically, in some cases when premon- itory visual disturbances have been present and carotid thrombosis finally occurs with contralateral hemiplegia, the vision may re- main unimpaired, as adequate time has elapsed for collateral circulation to maintain blood flow to the retinae.

A PHYSICIAN: What about the results of surgery and anticoagulant therapy?

DR. CREVASSE: As in this case, in general, the surgical results have been disappointing. When symptoms are present with carotid thrombosis, the collateral circulation through the basilar and opposite carotid is impaired. This concept is substantiated by the high incidence of asymptomatic carotid thrombosis and the tilt-table experiments on otherwise normal persons with carotid artery ligations without symptoms.

Rob and Wheeler[11] have reported the gest successful series of operated cases. ey have employed direct arterial surgery th and without hypothermia to restore blood w through a partially or completely ob- ucted carotid in a total of 27 patients. even of this series had partial occlusion th transient neurologic symptoms. They re able to re-establish good blood flow in of these. Four patients became asympto- tic, 2 improved, and 4 showed no change. There was one death. Of the 16 patients with complete occlusion, good blood flow could be re-established in only 4 patients. After complete occlusion, as in the preceding case, blood flow could be re-established only during a short interval before the clot ex- tended higher into the cranial cavity. In the group of complete occlusion only 1 patient became asymptomatic and the remaining 13 showed no change. There were 2 deaths. It seems that the patients most likely to benefit from surgery are those with incomplete occlu- sions who consult their physician because of transient symptoms of cerebrovascular insuffi- ciency. This is the group in whom the neuro- logic examination will most likely be negative and the only physical finding may be a systolic or continuous murmur over the partially ob- structed carotid, usually contralateral to neurologic symptoms. Restoration of flow in these patients will be rewarding not only in frequently relieving symptoms of cerebral vascular insufficiency but may in turn prevent the later development of complete thrombosis and irreversible neurologic deficits.

Though long-term follow-up and double- blind studies are not complete, promising results are seen with anticoagulants,[12] which appear to be the medical treatment of choice at the moment. In our experience, symp- toms of cerebral vascular insufficiency dimin- ish, and the neurologic status appears to stabilize after anticoagulation.

The rational and beneficial effects are not entirely clear. Anticoagulation may further delay occlusion of a partially obstructed carotid or prevent extension of the thrombus into the cranial cavity. Autopsy material[1] has revealed formation of thrombi in the carotid bulb and embolization of the ipsilat- eral cerebral hemispheres. Anticoagulation would appear more specific in this situation.

A PHYSICIAN: What is the prognosis of this syndrome?

DR. CREVASSE: Again, long-term follow-up studies in large series of patients are inade- quate, and the relative prognosis is unknown. However, in a review of 107 cases of complete occlusion of the carotid artery, Johnson and Walker[3] reported 15 per cent mortality with-

in several months, 15 per cent revealed no essential change, and 25 per cent showed improvement over varying periods of time. There was no follow-up study of the remaining patients. The follow-up of patients treated by anticoagulants and surgical reconstruction is again limited and inadequate. It appears, however, that their prognosis will be somewhat improved by these methods.

Case 5

E.S., a 56-year-old white woman, gave a history of benign hypertension for several years. Four weeks ago the patient developed typical angina pectoris precipitated by exertion and relieved promptly by nitroglycerin. There was no history of neurologic symptoms or visual disturbances although there had been slight impairment of memory in the past few months.

Her father died at age 45 of high blood pressure and cerebral vascular accident. Her mother died at age 59 of coronary artery disease.

The blood pressure was 160/90. The carotids pulsated vigorously to the angle of the jaw. Over the right carotid bulb a loud continuous murmur was present. This murmur was hemodynamically identical with the continuous murmur in case 1 and figure 3. There was no bruit over the head or the left carotid artery. Pharyngeal palpation of the internal carotids revealed diminished pulsations bilaterally, with no obvious asymmetry. The heart revealed a grade II aortic and mitral systolic murmur. The neurologic examination was completely negative.

DR. CREVASSE: Approximately 3 per cent of Fisher's unselected autopsy series had severe stenosis of the carotids and 11 of Rob's 27 operated cases had partial occlusion with neurologic symptoms. The pathophysiologic counterpart of these findings may be a systolic or continuous murmur over the carotid bulb, the most common site of involvement.

We have recently correlated the frequency and significance of *localized* carotid murmurs in 100 consecutive general hospital patients. Well localized systolic murmurs were heard over the carotid in 7 and continuous murmurs were present in 2. These murmurs occurred both in asymptomatic patients and patients with overt carotid artery insufficiency as in cases 1, 2, 4, and 5. In a 4-month period we have observed a well-localized continuous murmur over the carotid bulb in 8 patients. Five of these patients had neurologic symptoms or deficits, usually on the side opposite the carotid murmur.

The final clinical spectrum of carotid artery insufficiency and thrombosis has yet to be defined. The initial evidence of carotid obstruction may be localized murmurs over the carotid bulb and these may be noted prior to the development of symptoms. The patients may complain of "swishing sounds" or roaring in the head. When complete thrombosis ensues, the head noises and bruits cease and neurologic symptoms may appear, depending on alterations in blood flow and adequacy of collateral circulation.

A PHYSICIAN: What are the mechanisms responsible for the bruits heard in these patients?

DR. HURST: One can divide the bruits heard in these patients into those heard in the head and those in the neck. The examiner should establish the habit of listening over the cranium and especially over the eyeballs, in patients suspected of carotid insufficiency. It is a good plan to have the patient close his eyelids and place the bell of the stethoscope over 1 eye and have the patient "open" his eyes. This allows one to listen through a relaxed eyelid, thereby eliminating the sounds of muscle tremor.

The high-pitched bruit heard over the eyeball on the side opposite the carotid thrombosis (fig. 1) can be due to 1 of 2 mechanisms: 1. The retrobulbar arterial collateral circulation may be so abundant that a bruit is produced. 2. It is likely that a bruit produced by a partially occluded artery within the skull will be heard better over the nearest eyeball. In this case, the bony orbit acts as a megaphone. Intercranial arteriovenous fistulae and severe anemia can produce such murmurs but are not as common as vascular occlusive disease of the head and neck.

It is convenient to divide the murmurs in the neck into systolic and continuous murmurs.

Everyone is aware of the systolic arterial bruit heard in the neck vessels in patients with anemia, fever, thyrotoxicosis, and the other causes of high cardiac output. In the

absence of these conditions a systolic bruit in the carotid artery should force one to consider the murmur of aortic stenosis, which is frequently transmitted into the neck or carotid arterial obstruction. Aortic stenosis is usually heard best maximally over the primary aortic area, may be heard at the apex, and is transmitted up both carotids, diminishing in intensity as one approaches the angle of the jaw. When atherosclerosis of the carotids occurs without significant obstruction, the systolic bruit is seldom loud and occurs with equal intensity through both carotids. When one encounters a loud and *localized* systolic murmur in a carotid artery, this should be considered as an important diagnostic clue of partial occlusion of this vessel. The systolic bruit is heard over the site of the arterial narrowing and can, therefore, disappear if the occlusion becomes complete. Occasionally, in complete occlusion of one carotid artery, collateral blood flow is increased through the opposite carotid and if it is partially occluded, a systolic or continuous murmur may be detected over the opposite carotid. Occasionally a faint systolic murmur is present over the site of carotid occlusion. It can be obliterated by manual compression of the branches of the external carotid and is related to an increase in collateral flow through this vessel (fig. 1).

There are several causes of a continuous murmur in the neck. The most common cause is the normal venous hum that is usually heard in children and rarely heard in adults. This type of murmur can be eliminated or altered significantly by light pressure on the jugular veins and is seldom a diagnostic problem.

Graves' disease or an arteriovenous fistula between the carotid artery and jugular vein may cause a continuous murmur. One is usually able to identify systolic pulsations of the neighboring vein, and an increase in skin temperature and venous return in the latter.

A continuous murmur may be heard over an area of partial carotid occlusion when the collateral vessels are inadequate. Edholm et al.[13] have shown that localized or segmental obstruction in arteries has no effect on diastolic pressure distal to an obstruction producing only a systolic pressure gradient. Flow to the segment distal to the obstruction is provided by adequate collateral circulation and equal diastolic pressures are maintained both proximal and distal to the obstruction. The turbulence of flow in systole produced by the narrowed carotid and systolic pressure gradient accounts for the systolic bruit heard. Myers and co-workers[14] have made observations on continuous murmurs over partially occluded vessels, with particular reference to the aortic arch syndrome. The production of a similar hemodynamic situation in animals clearly substantiated their hypothesis that the continuous murmur was due simply to partial occlusion of a major artery under circumstances where collateral circulation was simultaneously diseased or inadequate to maintain diastolic pressure distal to the involved area. In this situation, a considerable pressure gradient exists both in systole and diastole, producing a continuous murmur over a partially occluded vessel. In carotid artery insufficiency when collateral circulation through the opposite carotid and the basilar system is inadequate, a continuous murmur is produced usually over the carotid bulb, the most common site of involvement (fig. 3). This is often confused with an arteriovenous fistula in the neck.

In summary, there are several points worth remembering. 1. Carotid artery thrombosis and stenosis is a common disease occurring in 9.5 per cent of one unselected autopsy series but is infrequently recognized clinically. 2. Physicians interested in cardiovascular disease are being confronted with this syndrome because of its relationship to changes in blood pressure and cardiac output. 3. The carotid arteries are neglected by the pathologist and are a no man's land between the internist and neurologist. Careful examination and auscultation of the head and neck are rewarding in "routine strokes" and may clarify bizarre neurologic symptoms in patients with cardiovascular disease. 4. A continuous machinery murmur may be present over a partially occluded carotid and is a valuable adjunct in the early recognition of

carotid artery insufficiency. 5. Carotid artery insufficiency is a treatable disease. Its early recognition and appropriate therapy before complete thrombosis occurs will directly influence the therapeutic results.

REFERENCES

1. Fisher, M.: Occlusion of the carotid arteries. Arch. Neurol. & Psychiat. **72**: 187, 1954.
2. Baldrey, E., Maass, L., and Miller, E.: The role of atlantoid compression in etiology of internal carotid thrombosis. J. Neurosurg. **13**: 127, 1956.
3. Johnson, H. C., and Walker, A. E.: The angiographic diagnosis of spontaneous thrombosis of the internal and common carotid arteries. J. Neurosurg. **8**: 631, 1951.
4. Dunning, H. S.: Detection of occlusion of the internal carotid artery by pharyngeal palpation. J.A.M.A. **152**: 321, 1953.
5. Cohen, J., and Miller, S.: Eyeball bruits. New England J. Med. **255**: 459, 1956.
6. Fisher, C. M.: Cranial bruit associated with occlusion of the internal carotid artery. Neurology **7**: 299, 1957.
7. Shanbrom, E., and Levy, L.: The role of systemic blood pressure in cerebral circulation in carotid and basilar artery thromboses. Am. J. Med. **23**: 197, 1957.
8. Meyer, J. S., Leiderman, H., and Denny-Brown, D.: Electroencephalographic study of insufficiency of the basilar and carotid arteries in man. Neurology **6**: 455, 1956.
9. Koch, F. L. P.: Ophthalmodynamometry. Arch. Ophthalmol. **34**: 234, 1945.
10. Heyman, A., Karp, H., and Bloor, B.: Determinations of retinal artery pressure in diagnosis of carotid artery occlusion. Neurology **7**: 97, 1957.
11. Rob, C., and Wheeler, E. B.: Thrombosis of internal carotid artery treated by arterial surgery. Brit. M. J. **2**: 264, 1957.
12. Millikan, C. H., Siekert, R. G., and Shick, R. M.: Studies in cerebral vascular disease V. The use of anticoagulants in the treatment of intermittent insufficiency of the internal carotid arterial system. Proc. Staff Meet., Mayo Clin. **30**: 578, 1955.
13. Edholm, O. G., Howarth, S., and Sharpey-Schafer, E. P.: Resting blood flow and blood pressure in limbs with arterial obstruction. Clin. Sc. **10**: 361, 1951.
14. Myers, J. D., Murdaugh, H. V., McIntosh, H. D., and Blaisdell, R. K.: Observations on continuous murmurs over partially obstructed arteries. Arch. Int. Med. **97**: 726, 1956.

Rob, C., and Wheeler, E. B.: Thrombosis of Internal Carotid Artery Treated by Arterial Surgery. Brit. M. J. **2**: 264 (Aug. 3), 1957.

In 27 patients with symptomatic occlusions of the internal carotid artery direct arterial surgery was performed in an attempt to restore adequate blood flow. A good blood flow was obtained in all 11 patients with partial occlusion, and in only 4 of the 16 with complete occlusions. In complete occlusions blood flow could only be reestablished during the short period before the clot extended into the cranial cavity, but even then irreversible cortical damage might have occurred. The risk of surgery is not too great in these patients since only 2 of the 27 patients so treated had any postoperative exacerbation of their neurologic symptoms. The authors believe that the patients most likely to benefit from such surgery are those with incomplete occlusions who have symptoms of cerebrovascular insufficiency. In these patients restoration of adequate blood flow not only frequently relieves the symptoms but also may prevent the later development of complete thrombosis and irreversible brain damage.

Sagall

CLINICAL PROGRESS

The Survival of Excitability, Energy Production and Energy Utilization of the Heart

By MILTON KARDESCH, M.D., CHARLES E. HOGANCAMP, M.D., AND RICHARD J. BING, M.D.

AFTER death of the organism, when heart beat or respiration ceases, many biological processes continue for a considerable period of time. The difference in survival depends, in all probability, on the resistance of the biochemical and biophysical processes to anoxia. Since life is the result of equilibrium and balance, the deterioration of any one of these vital functions results in destruction of the whole. This concept applies to the organism as well as to individual organs. For example, it has been shown[1] that the contractility of heart muscle persists for at least 6 hours after death of the patient, in contrast to cardiac excitability, which is rapidly altered by myocardial ischemia and anoxia.[2] The following review deals with the resistance of processes concerned with energy production, energy utilization and excitability of heart muscle to anoxia. Data presented here have been compiled from work carried out in this laboratory and from the literature.

ENERGY PRODUCTION

Energy Production in the Heart. The synthesis of adenosinetriphosphate (ATP), the primary energy carrier between the energy-yielding sources and the energy-requiring functions, is localized in the mitochondria. These structures, called sarcosomes in the heart muscle, are the power plant of the cell, in which the enzymes of the tricarboxylic-acid cycle, of the electron transfer system and of oxidative phosphorylation are localized.[3] Studies with the electron microscope have revealed that the sarcosomes of cardiac muscle are contiguous to the A bands of the myofibrils, indicating the close relationship between the site of energy production and the biostructures of energy utilization.[4–6] Previous studies from this laboratory with the technic of coronary sinus catheterization have shown that under normal resting conditions the myocardium extracts significant amounts of glucose, pyruvate, lactate, fatty acids, ketones and amino acids from coronary blood.[7–9] Other technics, such as the heart-lung preparation and the use of tissue slices and homogenates, have also substantiated the fact that these foodstuffs serve as oxidizable substrate for heart muscle.[10, 11–13] As with the intact heart in situ, the extent of extraction of each foodstuff by cardiac muscle slices appears to depend on the concentration in the blood or surrounding medium.[7, 8, 14] In the postabsorptive state, the human heart derives on the average 70 per cent of its energy requirements from noncarbohydrate material, chiefly fatty acids.[8] Total myocardial energy production can be measured by determining the oxygen consumption of the heart, provided glycolysis is absent. In addition, determinations of individual enzyme systems in heart muscle give more detailed information on the possible changes in intermediary metabolism.

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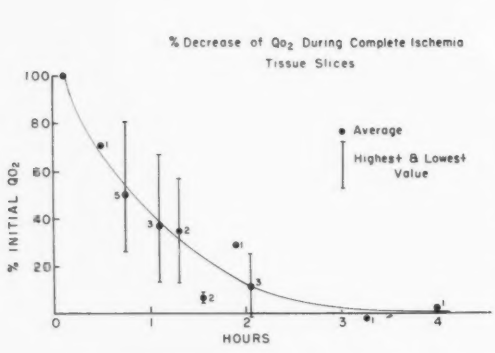

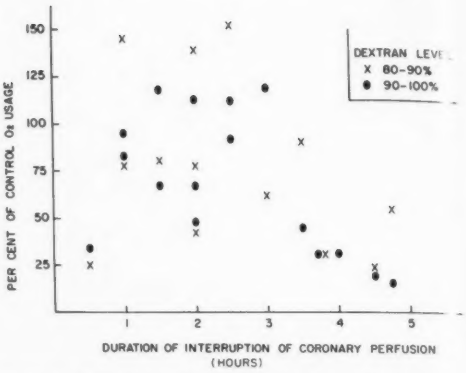

FIG. 1 *Left.* Shows the Qo_2 of heart muscle slices removed from hearts of animals at varying intervals after death. One hour after death only 40 per cent of the initial Qo_2 remains.

FIG. 2 *Right.* Illustrates the relationship of duration of interruption of coronary perfusion through the arrested heart in situ to the per cent of control oxygen usage. Only data were selected in which recovery of dextran in coronary sinus blood was above 80 per cent in order to eliminate admixture of blood appearing in the coronary sinus originating from the ventricular cavities. It may be seen that the control levels of oxygen usage were maintained for about 2½ hours; longer interruption of perfusion resulted in a decline in myocardial oxygen usage.

Survival of Energy Production. The effects of complete myocardial ischemia and anoxia on heart muscle have been investigated by various technics. Webb et al.[15] have reported a depression of respiration of rat heart muscle slices made anoxic in the Warburg apparatus. Anoxic states were produced by gassing the Warburg vessels with nitrogen. A period of 20 minutes of anoxia was found to reduce the oxygen uptake to 40 per cent of the control. After 60 minutes of anoxia, there was a reduction in Qo_2 to 23 per cent of the control. However, when the heart remained in the animal after decapitation, a more rapid progression of metabolic changes occurred; thus, after 15 minutes, the Qo_2 of rat heart muscle slices had declined to 24 per cent of the control value. Fuhrman et al.,[16] also using rat heart slices immediately after decapitation, showed that 40 minutes of complete anoxia in an atmosphere of nitrogen was sufficient to abolish completely the subsequent uptake of oxygen. In addition, Pearson and associates[13] using rat heart slices induced anoxic states by suddenly shutting off the oxygen supply to the tissue. Within 10 minutes the rate of respiration was reduced by 40 per cent of the control value; at the end of 20 minutes a 47 per cent change in the oxygen consumption was observed. Fuhrman et al.[17] have reported similar findings in rat heart slices prepared from animals dying in a decompression chamber in which the oxygen consumed was replaced by nitrogen. The oxygen consumption of cardiac muscles at the time of death had decreased to 35 per cent of the control values. Similar results were recently reported from this laboratory.[18] Slices of dog heart muscle were removed immediately after death and transferred into Warburg vessels. After periods ranging from 30 minutes to 4 hours, other samples were removed from the same heart and their respiration was determined. Thus each animal served as its own control. After 1 hour of anoxia the oxygen consumption of heart muscle slices was found diminished to 40 per cent of the control value (fig. 1).[18] Fuhrman et al.[16] found that a reduction of the partial pressure of oxygen content to values below 100 per cent but above 20 per cent diminished the Qo_2 of slices of rat hearts within 20 minutes. Similar observations were made by Furchgott and Shorr,[19] who discovered that slices of dog hearts maintained at

20 per cent oxygen in the Warburg apparatus showed a reduction in Qo_2 of 55 per cent as compared to the Qo_2 measured in an atmosphere of 100 per cent oxygen.

The effects of complete anoxia on the myocardium of the arrested dog heart perfused in situ have also been investigated in this laboratory.[19] The technic by which the study of the arrested heart was accomplished has been described in detail elsewhere.[18] In principle, all coronary arteries of the arrested heart of the closed-chest dog were perfused through a special catheter. The oxygen use of the arrested perfused heart remained at control levels as long as the interruption of the coronary circulation did not exceed 2 hours. Longer interruption of perfusion resulted in a rapid diminution of myocardial oxygen use, and after 4 to 5 hours of ischemia all myocardial oxygen consumption ceased (fig. 2). The interruption of the coronary circulation resulted in a significant disturbance in the myocardial extraction of carbohydrates. There was an increase in the myocardial lactate production, probably resulting from myocardial anoxia. After 4 hours of complete myocardial ischemia, myocardial oxygen use declined proportionately more than myocardial glucose use, probably as a result of anaerobic glycolysis.[18]

The data presented here reveal a more rapid decline in oxygen consumption of heart muscle slices and heart homogenates than of the whole arrested heart. It is likely that many factors account for this difference. Metabolic studies on the arrested heart in situ have the advantage of being carried out in a more physiologic and relatively less disturbed environment. In contrast, in heart muscle slices varying degrees of anoxia are always present because of the time required for the preparation of tissue slices and homogenates. In addition, the homogenizing or slicing of tissues may damage a number of cells and further depress the oxygen consumption. Slices prepared from hearts remaining in the dead animal for varying periods of time show evidence of glycolytic respiration, although the surrounding gas phase in the Warburg apparatus consists of

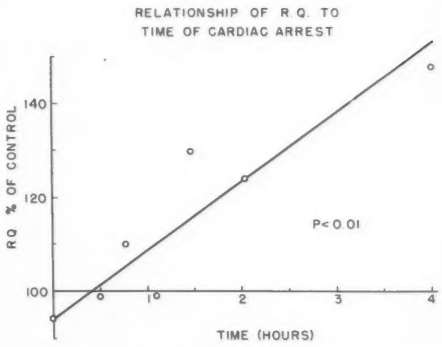

FIG. 3. Describes the positive relationship between respiratory quotient (expressed in per cent of control value) of heart muscle slices and the time after death at which the slices were prepared. The rise in respiratory quotient is probably the result of release of lactic acid into the buffer solution.

100 per cent oxygen. The theoretical respiratory quotient of these slices in media with high glucose concentrations should be unity. However, in these instances the respiratory quotient was found elevated to 1.2; there was also a significant relationship between the height of the respiratory quotient and the duration of cardiac arrest (fig. 3). It is likely that the lactate produced originated under aerobic conditions in the Warburg vessel rather than in the anoxic whole heart. This aerobic glycolysis may be evidence of the severe metabolic damage incurred during the prolonged period of anoxia.[18]

The lack of resistance of heart muscle slices to the effects of short periods of anoxia appears to be the result of injury to essential enzymes and co-enzymes. Which of these enzymes or co-enzymes are most vulnerable to anoxia has been the subject of much controversy. Bernheim and Bernheim[20] reported that rat heart slices, although exhibiting a depressed respiration after semianaerobic incubation, are capable of oxidizing succinic acid at a rate equal to that demonstrated by fresh slices. These authors concluded, therefore, that carbohydrate metabolism was disturbed at some stage between hexose phosphate and lactic and pyruvic acid. Govier[21] found that when homogenates of heart muscle

remained within the body at room temperature for 1 hour, the diphosphopyridine nucleotide and cocarboxylase activity diminished only to 23 per cent and 13 per cent respectively. Similar findings have been reported for heart homogenates from hypoxic dogs or animals in hemorrhagic shock.[22, 23] In contrast, ligation of a coronary artery resulted, after 2 hours, in a diminution in myocardial diphosphopyridine nucleotide activity to 83 per cent of the control value with no change in the cocarboxylase activity.[22] Similarly, Lenley and Meneeley[25] have reported a significant decrease in diphosphopyridine nucleotide and cytochrome C activity in heart homogenates prepared from rats killed by acute anoxia in the low-pressure chamber. Biorck[26] found no significant difference between the cytochrome C content of fresh human heart specimens taken during cardiac surgery and autopsy material. However, Mengebier[27] has demonstrated a decrease in the cytochrome C-cytochrome oxidase activity of rat heart homogenates exposed to nitrogen for 30 minutes only. In contrast, malic-acid dehydrogenase activity in hearts of rats exposed to acute anoxia was not significantly different from the control value.

Much of the reported variability in the survival time of the respiratory enzymes and co-enzymes may be attributed to differences in technics. Some investigators used heart muscle slices, others heart homogenates. Variations in the Warburg media, buffers, gas mixtures, and the substrates and enzymes used to fortify the media may also account for the different results. In addition, preparations were obtained from a variety of animal species and the durations and degrees of anoxia differed.

Histochemical and electron microscope studies have also been used in the study of the effect of anoxia on the heart. In anoxic heart muscle fibers undergoing necrobiotic changes, stainable muscle glycogen diminished within 20 to 45 minutes after the onset of myocardial anoxia. Most of the glycogen had disappeared within 4 to 5 hours following complete anoxia.[28, 29] Similar findings were observed by other workers.[30–32] Stainable desoxyribonucleic acid can be demonstrated 6 to 12 hours after myocardial anoxia, and specific stains for succinic dehydrogenase are positive for as late as 12 to 15 hours after.[33] The structure of mitochondria of heart muscle also changes during anoxia. Mitochondria assume a swollen crescent shape as their oxygen uptake diminishes.[34–36]

Cardiac Excitability

Excitation in Heart Muscle. The function of excitation and the rapid spread of electric activity throughout the muscle cell is related to reactions taking place at the cell membrane. The membrane also plays an important role in maintaining chemical and electric potential differences between the interior of the cell and the surrounding fluid, by preserving a selective permeability for electrolytes.[37] Electron microscope studies have revealed the membrane to be a discrete double-layered complex with several folds and interspaces.[38] The property of permeability of the cell membrane has given rise to many theories of its functional structure. The membrane has been considered a bimolecular or multimolecular sheath or a structure of many pores of different sizes.[39, 40] The functional structure of the cell membrane has also been described wholly in terms of its electric properties.[37, 41]

The development of the improved micropuncture technic by Ling and Gerard in 1949[42] now permits a more direct observation of changing electric characteristics of the cell membrane. Action potentials can thus be recorded from the interior of the cell. In addition, the membrane resting potential, the potential difference across a limited area of the resting cell membrane, can also be measured. The ratio of the intracellular to extracellular K^+ ion concentrations is probably the determining factor concerned with the magnitude of this resting potential.[42–44] Studies of the influence of extracellular ionic concentrations and of metabolic inhibitors on transmembrane ionic movements suggest the existence of active metabolic processes of the membrane itself (sodium-potassium pump)

operating during the resting phase.[45–47] On excitation the stimulus lowers the membrane potential resulting in the rising phase of depolarization with a reversal of the negative membrane resting potential to that of a positive overshoot.[48] The positive spike is then abolished, so that the membrane potential is restored to the resting level.[45] The production of action potentials and the propagation of electric stimuli appear rather to arise from increases in permeability that permit ions to move downward across their respective concentration gradients than to arise from metabolic energy.[37]

Survival of Cardiac Excitability. The survival of cardiac excitability has been studied with the microelectrode technic by several investigators. Webb and Hollander[49] have determined the membrane potentials of isolated, electrically stimulated anoxic rat atria. The height of the action potentials fell after 4 minutes of anoxia. However, contractility diminished within 1 to 2 minutes, progressing to complete cessation of activity 15 to 20 minutes later. The action potential shortened after a brief period of anoxia, but the membrane resting potential diminished only slightly. No action potentials were elicited after 17 minutes. Trautwein and Dudel[50] studied the effects of anoxia on the membrane action potential and contractility of cat papillary muscles. These muscle strips were stimulated electrically and gassed with 95 per cent nitrogen in a chamber with a continuously flowing stream of Tyrode's solution. At low oxygen tensions, the duration of the action potential shortened rapidly, followed by a diminution in the amplitude. Action potentials could be elicited for at least 32 minutes after the onset of anoxia. Within 5 minutes after the introduction of nitrogen, the amplitude of the contractions decreased to one half of their control values; after 30 minutes they had diminished to one sixth of the control value. The relaxation period was prolonged as anoxia continued.

The effects of complete ischemia on the spontaneous ventricular action and resting potentials were studied in this laboratory.[1,2]

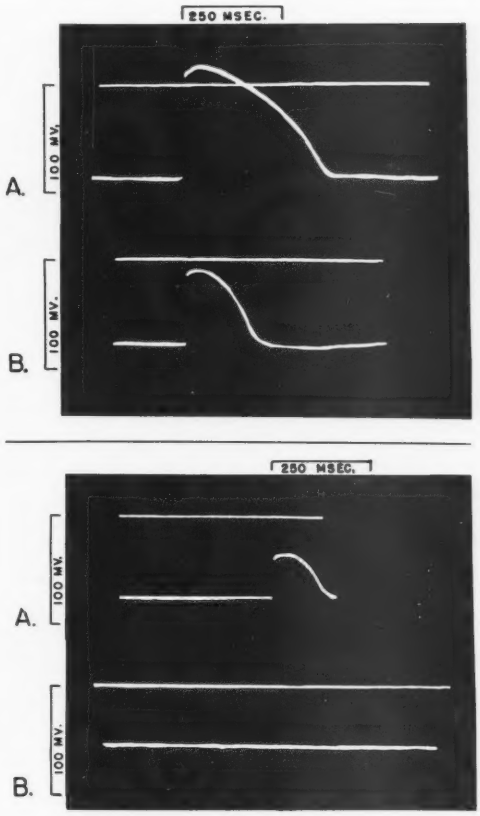

FIG. 4 *Top. A.* Illustrates a normal action potential. The rapid depolarization and slow phase of repolarization and the overshoot are visualized. The resting potential is approximately 85 mv. *B.* The action potential after 13 minutes of complete interruption of the coronary circulation. There is a decline in amplitude and duration of the action potential.

FIG. 5 *Bottom. A.* Illustrates the effect of complete coronary ischemia on the action potential after 18 minutes of complete interruption of the coronary circulation. The fall in the height of the action potential and the decline in duration are conspicuous. There is some loss in the height of the resting potential. *B.* Illustrates the decline in the height of the membrane resting potential 25 minutes after interruption of the coronary circulation.

Dog and rabbit hearts, excised and bathed in oxygenated Tyrode's solution, were perfused with a mixture of blood and Tyrode's solution by means of a modified Langendorff technic. A shortening of the action potential was ob-

served 4 minutes after interruption of the coronary circulation. The amplitude of the transmembrane resting potential fell to an average of 65 per cent of the control value at the time of complete cessation of electric activity. After 20 minutes of complete ischemia, all spontaneous mechanical and electric activity ceased (fig. 4 and 5). The diminution of the duration of the action potential was due to a shortening of the repolarization phase of the action potential; this fact suggests a more rapid passive transport of K^+ ions outwardly across its concentration gradient. Weidman[51] speculated that this shortening of repolarization during anoxia results from a rising extracellular K^+ ion concentration. The diminution of the amplitude of the transmembrane resting potential during anoxia could result from an increased uptake of sodium and consequent loss of potassium by the cell during recovery.[52-54] The fall in the amplitude of the action potential can be related to the effects of the lowered resting potential. Voltage clamp studies[55] with mammalian Purkinje fibers have shown that the capacity for an increase in sodium ion permeability is related to the level of the membrane potential before stimulation.

It is probable that the alterations, induced by anoxia, in the ionic transfer across the cell membrane were closely related to the high-energy phosphate concentration. The membrane resting potential of mammalian cardiac fibers is lowered greatly by prolonged anoxia or by metabolic inhibitors.[51, 56] The action of metabolic inhibitors on the resting potential of squid axons for periods longer than 1 hour produces a progressive decline in the efflux of labeled sodium and in the uptake of labeled potassium ions during the resting phase, with little or no effect on the sodium ion influx or potassium ion outflow during the action potential. Axons treated in this manner are capable of propagating normal action potentials after electric stimulation.[47] Electrically stimulated cat papillary muscles contracting in the absence of oxygen showed a moderate decrease of creatine phosphate and a significant diminution of ATP and of total adenosine nucleotides. A decline in the force of contraction of anoxic muscles accompanied the fall in ATP concentration.[57] Thus Long and Gerard,[56] using anoxic single frog sartorius fibers, showed a parallel fall in phosphocreatine and membrane potential during a 3-hour period of observation. The question of the location of the ATP generating system for the maintenance of membrane electric potential itself has not as yet been answered.

Energy Utilization

Energy Utilization in Heart Muscle. In its structure heart muscle does not differ extensively from skeletal muscle; functionally it also possesses the same basic mechanisms of motion.[58] The discovery that the muscle proteins, actin and myosin, combine to form actomyosin complex, the contractile protein in muscle, has shed much light on the nature of the alterations occurring in contracting muscles at the molecular level.[59] Szent-Gyorgyi stated[60] that the myosin molecules generate electrically negative charges that act as repulsive forces keeping the myosin particles from folding during the resting state. These negative charges are balanced by a surrounding atmosphere of potassium ions. Upon contraction, the charged state of the actomyosin complex dissipates, causing the potassium ions to be set free and to diffuse outwardly through the depolarized cell membrane. The net result is then a folding of the muscle protein during shortening.

During life, adequate oxygen and nutrients made available to the heart by its abundant blood supply, insure a sufficient production of high-energy phosphates by the respiratory enzymes. Because heart muscle demands an uninterrupted activity, this organ must continuously synthesize a constant supply of energy-yielding ATP as fast as it is used.[61] The rate of dephosphorylation of ATP determines the rate of ATP synthesis. The disappearance of ATP from muscle is determined by the magnitude of the reserve of fuel supply and of high-energy phosphate bonds such as phosphocreatine.[62, 63] A number of workers have demonstrated that the phosphocreatine

content of heart muscle is much lower than that in skeletal muscle.[64-68] This indicates that the reserve of high-energy phosphate in heart muscle is low and that ATP has to be rapidly synthesized. During contraction, ATP dissociates actomyosin into myosin and actin. Simultaneously, ATP is split into adenosinediphosphate and inorganic phosphate.[69]

Survival of Energy Utilization. The most conspicuous change after death is the stiffening of the heart muscle during rigor mortis. For many years such a change has been explained on a chemical basis as a coagulation of the proteins by the lactic acid produced after death. However, Hoet and Marks[70] demonstrated in 1926 that rigor occurred in animals dying of excessive amounts of insulin in the complete absence of any acid. These findings were confirmed by Bate-Smith and Bendall,[71] studying the process of stiffening of muscles undergoing rigor in terms of the extension of the muscle by an applied load.

After death and during extreme anoxia, the most striking chemical changes in muscle are the production of lactic acid by anaerobic glycolysis, the rapid breakdown of phosphocreatine, and the subsequent dephosphorylation of ATP.[57, 72-75] Studies by Erdos[72] revealed a close parallel between the hardness of muscles in rigor and the ATP concentration. At maximum rigor virtually no ATP is present in muscle. Greiner,[57] studying anoxic cat papillary muscles, reported a significant elevation of inorganic phosphate and a decrease of phosphocreatine. He also noted a significant diminution of ATP and of the total quantity of adenosine nucleotides, while the concentration of adenosine monophosphate and diphosphate rose. Szent-Gyorgyi[76] found that the ATP level in normal heart muscle is the same as in skeletal muscle. However, the initial concentration of ATP in heart muscle was maintained for no more than 10 minutes after death as compared to from 80 to 140 minutes reported for skeletal muscles.[64, 77] In these experiments, muscle strips were periodically loaded in an anaerobic atmosphere. The rapid phase of rigor mortis in heart muscle began 50 minutes after death, as compared to from 150 to 250 minutes in skeletal muscle.[64, 75] At that time, the myocardial ATP concentration had fallen to 50 per cent of its initial value. The delay period of 50 minutes implies a slow destruction of ATP. As there is very little phosphocreatine in heart muscle, the ATP is synthesized by glycolysis during this period, and therefore is closely related to the glycogen stores of the myocardium.[64] This relation has been shown to hold, irrespective of the muscle pH at the onset of rigor mortis.[77]

The shortening that accompanies rigor mortis appears to be similar to that associated with the structural changes in the myofibrils during physiologic contraction. Myofibrils, isolated from muscles in rigor and studied by electron microscopy, reveal shortened I bands characteristic of contracted myofibrils.[78] However, the work done by the muscle undergoing rigor is considerably less than that during physiologic contractions.[79] The decreasing extensibility of the muscle in rigor is ascribed to the formation of cross linkages between the active groups of actin and myosin components of the myofibril in the presence of a diminished ATP.[75, 80] Such an altered structural state would resist any changes in the length of the myofibrils that result from a sliding of actin filaments in between myosin filaments.[80]

The condition of the heart muscle proteins before death appears to influence the rate at which these postmortem changes progress. As noted previously, the low phosphocreatine concentration in heart muscle suggests that ATP is synthesized by glycolysis during the delay period of rigor mortis. In muscles rich in glycogen, these postmortem changes in the extensibility of muscle are considerably delayed.[81] Bate-Smith and Bendall[77] have shown that ATP disappears most rapidly at a pH of 6.3. Under these conditions, the soluble adenosinetriphosphatase is at its maximal activity. The initial pH of skeletal muscle is chiefly dependent upon the nature of the death struggle, whereas the ultimate pH is determined by the level of glycogen present immediately before death. Increasing

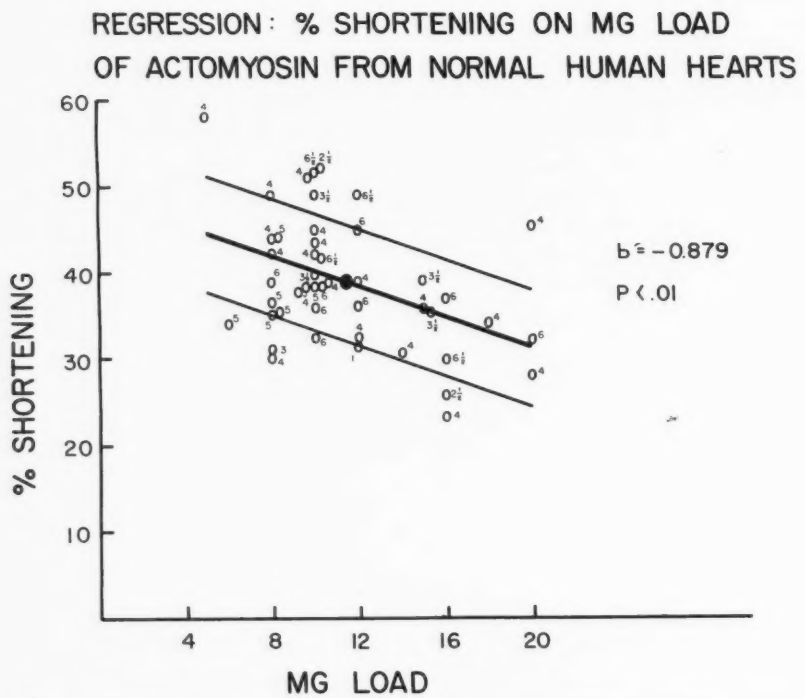

FIG. 6. Shows the relationship between milligram load and percentage shortening of actomyosin bands prepared at varying intervals after death of the patient. This is illustrated by the figure adjacent to the individual circles. The interval between death and preparation of actomyosin does not appear to influence contractility.

temperatures at the time of death appear to decrease the duration of the delayed period of rigor mortis.

The survival of contractile proteins of human heart muscle can be studied in models involving the contractility of actomyosin bands obtained from heart muscle homogenates and prepared at varying intervals after death of the patient.[1,82] These bands can be made to contract upon the addition of ATP. Provided the ionic environment surrounding the actomyosin band remains constant and of a composition at which maximal contraction can be obtained, the shortening of actomyosin bands is influenced by the weight with which the band is loaded and by inherent changes in contractility of the preparation. An inverse relationship exists between the load and the percentage of contraction.[82] Usually the contraction of actomyosin upon the addition of ATP, aside from being influenced by salt concentration and the load against which it is contracting, is of an "all or none" character.[69] This fact does not appear to be altered by the interval between death of the organism and the time of preparation of the protein complex. Thus recent studies from this laboratory have demonstrated that cardiac actomyosin exhibits considerable resistance to autolysis (fig. 6). There was no significant difference between the fresh preparation and that obtained from 1 to 6 hours after death of the patient.[1,82]

The preceding discussion has illustrated the difference in survival time of the 3 major biological functions of the anoxic heart muscle. Cardiac excitability is most vulnerable, while energy production and particularly energy utilization survive longer. The ability of any organ to function, just as of the whole

organism, depends upon the resistance of its weakest link. Therefore, the loss of excitability of cardiac muscle which is rapidly induced by ischemia leads to death of the whole organism, despite the ability of other biochemical and biophysical functions to survive for longer periods of time.

REFERENCES

1. Bing, R. J., Kardesch, M., Hogancamp, C. E., and Michal, G.: The survival of excitability, energy production and energy utilization of the heart. Tr. A. Am. Physicians. In press.
2. Kardesch, M., Hogancamp, C. E., and Bing, R. J.: The effect of complete ischemia on the intracellular electrical activity of the whole mammalian heart. Circulation Research. In press.
3. Green, D. E.: Organized enzyme systems. Texas Rep. Biol. & Med. **12**: 284, 1954.
4. Price, K. C., Weiss, J. M., Hata, D., and Smith, J.: Experimental needle biopsy of the myocardium of dogs with particular reference to histologic study by electron microscopy. J. Exper. Med. **101**: 687, 1955.
5. Harman, J. W., and Feigelson, M.: The cytological localization of mitochondria in heart muscle. Exper. Cell. Research **3**: 47, 1952.
6. Slater, E. C.: Mechanism of phosphorylation in the respiratory chain. Nature **172**: 975, 1953.
7. Bing, R. J., Siegel, A. L., Vitale, A., Balboni, F., Sparks, E., Taeschler, M., Klapper, M., and Edwards, W. S.: Metabolic studies on the human heart in vivo. I. Studies on carbohydrate metabolism of the human heart. Am. J. Med. **15**: 284, 1953.
8. —, —, Ungar, I., and Gilbert, M.: Metabolism of the human heart. II. Studies on fat, ketone, and amino acid metabolism. Am. J. Med. **16**: 504, 1954.
9. Ungar, I., Gilbert, M., Siegel, A. L., Blain, J. M., and Bing, R. J.: Studies on myocardial metabolism. IV. Myocardial metabolism in diabetes. Am. J. Med. **18**: 385, 1955.
10. McGinty, D. A., and Miller, A. T.: Studies on the coronary circulation. II. Absorption of lactic acid and glucose and the gaseous exchange of heart muscle. Am. J. Physiol. **103**: 712, 1933.
11. Braun-Menéndez, E., Chute, A. D., and Gregory, R. A.: Usage of pyruvic acid by the dog's heart. Quart. J. Physiol. **29**: 91, 1939.
12. Lehninger, A. L.: The oxidation of higher fatty acids in heart muscle suspensions. J. Biol. Chem. **165**: 131, 1946.
13. Pearson, O. H., Hastings, A. B., and Bunting, H.: Metabolism of cardiac muscle: Utilization of C-13 labeled pyruvate and acetate by rat heart slices. Am. J. Physiol. **158**: 251, 1949.
14. Olson, R. E., and Schwartz, W. B.: Myocardial metabolism in congestive heart failure. Medicine **30**: 21, 1951.
15. Webb, J. L., Saunders, P. R., and Thiener, C. H.: The metabolism of the heart in relation to drug action. I. The endogenous aerobic metabolism of rat heart slices. Arch. Biochem. **22**: 444, 1949.
16. Fuhrman, G. J., Fuhrman, F. A., and Field, J.: Metabolism of rat heart slices with special reference to effects of temperature and anoxia. Am. J. Physiol. **163**: 642, 1950.
17. —, —, and —: Oxygen consumption of excised rat tissue following acute anoxic anoxia. Am. J. Physiol. **144**: 87, 1945.
18. Michal, G., Beuren, A., Hogancamp, C. E., and Bing, R. J.: The effect of interruption of coronary circulation on the metabolism of the arrested heart. Am. J. Physiol. In press.
19. Furchgott, R. F., and Shorr, E.: The effect of succinate or respiration and certain metabolic processes of mammalian tissues at low oxygen tensions in vitro. J. Biol. Chem. **175**: 201, 1948.
20. Bernheim, F., and Bernheim, M. L. C.: The effect of various conditions on the respiration of rat heart muscle in vitro. Am. J. Physiol. **142**: 195, 1944.
21. Govier, W. M.: The destruction of coenzyme I and cocarboxylase in skeletal and cardiac muscle after death. Science **99**: 475, 1944.
22. Greig, M. E., and Govier, W. M.: The dephosphorylation of cocarboxylase in tissues during shock and anoxia. J. Pharmacol. & Exper. Therap. **79**: 169, 1943.
23. —: The destruction of cozyme and alloxazine adenine dinucleotide in tissues during shock. J. Pharmacol. & Exper. Therap. **81**: 164. 1944.
24. Govier, W. M.: The effect of experimental coronary artery ligation on the coenzyme I and cocarboxylase content of the myocardium of the dog. Am. Heart J. **29**: 384, 1945.
25. Lenley, J. M., and Meneeley, G. R.: Effects of anoxia on metabolism of myocardial tissue. Am. J. Physiol. **169**: 66, 1952.
26. Biorck, G.: The content of cytochrome C in

the human heart and skeletal muscle. Acta. med. scandinav. **154**: 305, 1956.

27. Mengebier, W. L.: Effects of anoxia on respiratory enzymes of the rat and hamster. Am. J. Physiol. **177**: 231, 1954.
28. Kent, S. P.: Effects of post mortem autolysis on certain histochemical reaction. Arch. Path. **64**: 17, 1957.
29. Yokoyama, H. O., Jennings, R. B., Clabough, G. F., and Wartman, W. B.: Histochemical studies of early experimental myocardial infarction. Arch. Path. **59**: 347, 1955.
30. Merrick, A. W.: Experimental coronary occlusion in dogs and its effect upon the cardiac glycogen fraction. Circulation Research **5**: 435, 1957.
31. Tennant, R., Grayzel, D. M., Sutherland, F. A., and Stringer, S. W.: Studies on experimental coronary occlusion. Chemical and anatomical changes in the myocardium after coronary ligation. Am. Heart J. **12**: 168, 1936.
32. Hermann, G., and Decherd, G.: Creatine and glycogen content of normal and infarcted heart muscle of the dog. Proc. Soc. Exper. Biol. & Med. **32**: 1304, 1935.
33. Wachstein, M., and Meisel, E.: Succinic dehydrogenase activity in myocardial infarction and in induced myocardial necrosis. Am. J. Path. **31**: 353, 1955.
34. Strawitz, J. G., and Hift, H.: Structure and function of mitochondria in irreversible hemorrhagic shock. Proc. Soc. Exper. Biol. & Med. **9**: 641, 1956.
35. —, and —: A study of mitochondrial changes in hemorrhagic shock. Surgical Forum **7**: 11, 1957.
36. Harman, J. W., and Feigelson, M.: The relationship of structure and function of mitochondria from heart muscle. Exper. Cell. Research **3**: 47, 1952.
37. Brooks, C. McC., Hoffman, B. F., Suckling, E. E., and Orias, O.: Excitability of the Heart. New York, Grune & Stratton, Inc., 1955.
38. Price, K. C., Weiss, J. M., Hata, D., and Smith, J. R.: Experimental needle biopsy of the myocardium of dog with particular reference to histologic study by electron microscopy. J. Exper. Med. **101**: 687, 1955.
39. Hober, R., Hitchcock, D. I., Bateman, J. B., and Fenn, W. O.: Physical Chemistry of Cells and Tissues. Philadelphia, Blakiston Company, 1945.
40. Davson, H., and Danielli, J. F.: The permeability of natural membranes. London, Cambridge University Press, 1952.
41. Lorente de No, R.: Studies from the Rockefeller Institute for Medical Research. B. **132**: 478, 1947.
42. Ling, G., and Gerard, R. W.: The normal membrane potential of frog sartorius fibers. J. Cell. & Comp. Physiol. **34**: 383, 1949.
43. Shanes, A. M.: A neglected factor in studies of potassium distribution in relation to the resting potential of nerve. J. Cell. & Comp. Physiol. **27**: 115, 1946.
44. Burgen, A. S., and Terraux, K. G.: The membrane resting and action potential of the cat auricle. J. Physiol. **119**: 139, 1953.
45. Hodgkins, A. L., and Huxley, A. F.: A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. **117**: 500, 1952.
46. Krogh, A., Lindberg, A. L., and Schmidt-Nielsen, B.: The exchange of ions between cells and extracellular fluid. II. The exchange of potassium and calcium between the frog heart muscle and the bathing fluid. Acta physiol. scandinav. **7**: 221, 1944.
47. Hodgkins, A. L., and Keynes, R. D.: Active transport of cations in giant axons from Sepia and Loligo. J. Physiol. **128**: 28, 1955.
48. —, Huxley, A. F., and Katz, B.: Measurements of current voltage relation in the membrane of the giant axon of Loligo. J. Physiol. **116**: 424, 1952.
49. Webb, J. L., and Hollander, P. B.: Metabolic aspects of the relationship between the contractility and membrane potentials of the rat atrium. Circulation Research **4**: 618, 1956.
50. Trautwein, W., and Dudel, J.: Aktions potential und Kontraktion des Herzmushel in Sauerstoffmangel. Pflüger's Arch. **263**: 23, **1956.**
51. Weidman, S.: Metabolic Aspects of Transport Across Cell Membranes. Madison, University of Wisconsin Press, 1957.
52. Hercus, V. M., Shirley, I., Katz, S. I., and McDowell, R. J. S.: Sodium exchanges in cardiac muscle. J. Physiol. **129**: 177, 1955.
53. Calkin, N., Taylor, I. M., and Hastings, A. B.: Potassium exchange in the isolated rat diaphragm. Am. J. Physiol. **177**: 211, 1954.
54. Blumgart, H. L., Gilligan, D. R., and Schlesinger, M. J.: Experimental studies on the effect of temporary occlusion of coronary arteries. Am. Heart J. **22**: 34, 1941.
55. Weidman, S.: The effect of the cardiac membrane potential on the rapid availability of

the sodium carrying system. J. Physiol. **127**: 213, 1955.

56. ...ING, G., AND GERARD, R. W.: The membrane potential and metabolism of muscle fibers. J. Cell. & Comp. Physiol. **34**: 413, 1949.

57. ...REINER, T.: The relationship of forces of contraction to high energy phosphate in heart muscle. J. Pharmacol. & Exper. Therap. **105**: 178, 1952.

58. SZENT-GYORGYI, A.: General views on the chemistry of muscle contraction. Adv. Cardiol. **1**: 6, 1956.

59. —: Studies on muscle. Acta physiol. scandinav. **9**, Suppl. 25, 1945.

60. —: Contraction in the heart muscle fiber. Bull. New York Acad. Med. **28**: 3, 1952.

61. WOLLENBERGER, A.: The energy metabolism of the failing heart and the metabolic action of the cardiac glycosides. Pharmacol. Rev. **1**: 311, 1949.

62. LOHMANN, K.: Ueber die enzymatische Aufspaltung der Kreatinphosphorsaeure; zugleich ein Beitrag zum Chemismus der Muskelkontraktion. Biochem. Ztschr. **271**: 264, 1934.

63. OLSON, R. E., AND SCHWARTZ, W. B.: Myocardial metabolism in congestive heart failure. Medicine **30**: 21, 1951.

64. LAWRIE, R. A.: The onset of rigor mortis in various muscles of the draught horse. J. Physiol. **121**: 275, 1953.

65. WOLLENBERGER, A.: On the energy-rich phosphate supply of the failing heart. Am. J. Physiol. **150**: 733, 1947.

66. DAVIES, F., FRANCIS, E. T. B., AND STOVER, H. B.: The distribution of nucleotide, phosphocreatine and glycogen in the heart. J. Physiol. **106**: 154, 1947.

67. FAWAZ, G., AND HAWA, E. S.: Phosphocreatine content of mammalian cardiac muscle. Proc. Soc. Exper. Biol. & Med. **84**: 277, 1953.

68. MYERS, V. C., AND MANGUM, G. H.: Some chemical observations on the human heart in health and disease. J. Lab. & Clin. Med. **26**: 199, 1940.

69. MOMMAERTS, W. F.: Muscular Contraction. New York, Interscience Publishers, 1950.

70. HOET, J. P., AND MARKS, H. P.: Observations on the onset of rigor mortis. Proc. Royal Soc. London **100**: 72, 1926.

71. BATE-SMITH, E. C., AND BENDALL, J. R.: Rigor mortis and ATP. J. Physiol. **106**: 177, 1947.

72. ERDOS, T.: Rigor contracture and ATP. Stud. Inst. Med. Chem. Univ. Szeged, Basel **3**: 51, 1943.

73. CHANG, I.: Asphyxial arrest of the isolated rabbit's auricle. Quart. J. Exper. Physiol. **27**: 113, 1937.

74. —: Effect of asphyxia on the ATP content of the rabbit's heart. Quart. J. Exper. Physiol. **23**: 3, 1938.

75. BENDALL, J. R.: The shortening of rabbit muscles during rigor mortis. J. Physiol. **114**: 71, 1951.

76. SZENT-GYORGYI, A.: Chemistry of Muscular Contraction. New York, Academic Press, Inc., 1947, p. 150.

77. BATE-SMITH, E. C., AND BENDALL, J. R.: Changes in muscle after death. Brit. Med. Bull. **12**: 230, 1956.

78. PERRY, S., AND HORNE, R. W.: The intracellular components of skeletal muscle. Biochem. et. Biophys. Acta **8**: 483, 1952.

79. SZENT-GYORGYI, A.: Free energy relations and contraction of actomyosin. Biol. Bull. **96**: 140, 1949.

80. HUXLEY, H., AND HANSON, J.: Changes in the cross striations of muscle during contraction and stretch and their structural interpretation. Nature **173**: 973, 1954.

81. BATE-SMITH, E. C., AND BENDALL, J. R.: Factors determining the time-course of rigor mortis. J. Physiol. **110**: 47, 1949.

82. KAKO, K., AND BING, R. J.: Contractility of actomyosin bands prepared from normal and failing human hearts. J. Clin. Invest. **37**: 465, 1958.

SECOND SYMPOSIUM ON CARDIOVASCULAR SOUND

Guest Editor: Victor A. McKusick, M. D.

This series of papers constituted the second Symposium on Cardiovascular Sound conducted in association with the Scientific Sessions of the American Heart Association. The symposium took place on Friday, October 25, 1957, at the Hotel Sherman in Chicago. The chairman of the morning sessions was Dr. Hans H. Hecht of Salt Lake City; Dr. J. Willis Hurst of Atlanta was chairman for the afternoon sessions. The first symposium was published in Circulation **16**: 270, and 414, 1957. This publication was made possible by a grant-in-aid from the National Heart Institute, U.S. Public Health Service, and by contributions from Mr. Arthur L. Humphries, The Rena and Walter Burke Foundation, Lakeside Laboratories, Burroughs-Wellcome Company, and the Wyeth Laboratories.

Endocardial and Intimal Lesions (Jet Impact) as Possible Sites of Origin of Murmurs

By JESSE E. EDWARDS, M.D., AND HOWARD B. BURCHELL, M.D.

UNDER certain circumstances, abnormal cardiovascular dynamics cause structural changes which remain in the necropsy specimen to invite postdictive interpretation of their relation to previously existing functional derangements. Among the more graphic of these imprints are the "jet" lesions. These are focal fibrous reactions in the linings of the heart or blood vessels which apparently result from trauma by repeated impacts of abnormal jetlike streams of blood.

The sites of such impacts are located where high-velocity streams of blood emanating from a high-pressure source and entering a relatively low-pressure compartment are suddenly either stopped or deflected. The vibration of the area and associated turbulence in the blood might be expected to cause a murmur. Since the jet lesions locate the sites of impact, they may be utilized as a tool for fruitful investigation when their position in the specimen is correlated with the other anatomic defects and the location of the previously recorded murmurs in the patient.

This presentation describes the positions of jet lesions encountered in a variety of cardiac and vascular disorders usually associated with stenotic orifices. Particular emphasis is placed on the variation in the positions of the jet lesions that have occurred in any one category of hemodynamic disturbance.

The variations in anatomic location of jet lesions at times correlate well with variations in position of maximal intensity of the murmurs for that condition during life.

The jet lesions, in addition to labeling the sites of possible origin of bruits, may be helpful in determining the previous pressure or the absence of regurgitant flow through a valve in the direction of blood flow that had existed in abnormal communications during the life of the patient.

NATURE OF JET LESIONS

The lesions of jet impacts have been variously designated as pockets of Zahn,[1] impingement plaques, endocardial pockets,[2-4] regurgitant lesions, frictional lesions,[5] and jet lesion

From the Mayo Clinic and the Mayo Foundation. The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

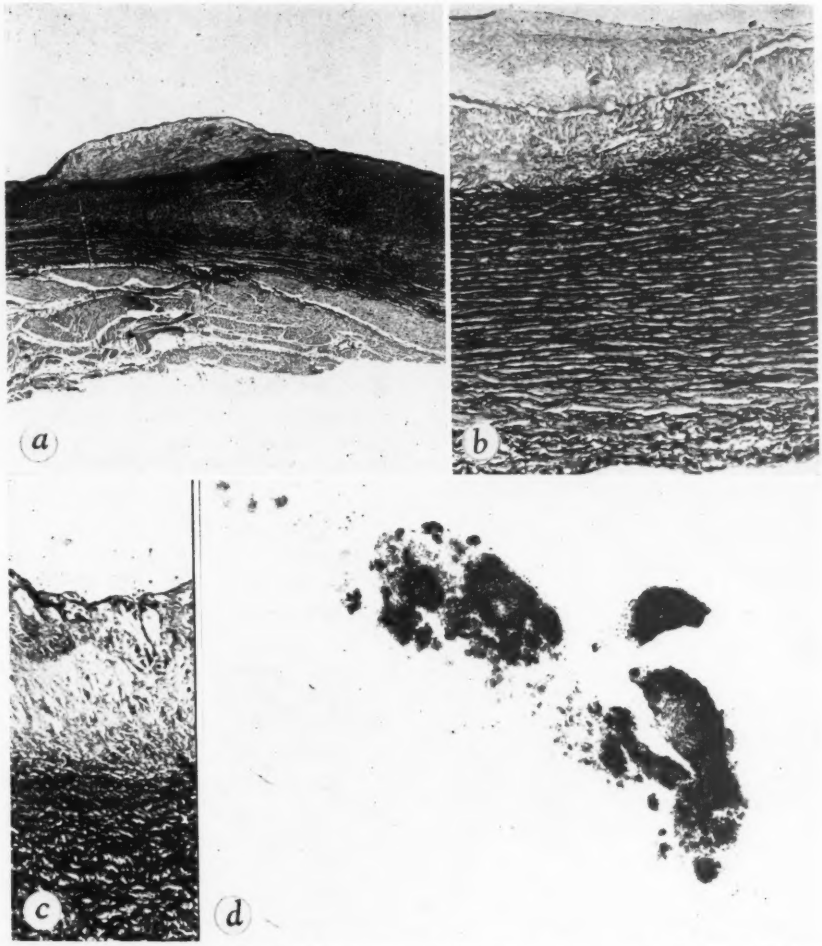

FIG. 1. Photomicrographs of jet lesions. *a.* Left atrium in a case of mitral insufficiency. Endocardial thickening by nonspecific fibrous tissue (Verhoeff's elastic-tissue stain, counterstained with van Gieson's connective-tissue stain; × 15). *b.* Ascending aorta in a case of aortic stenosis (ELVG; × 55). *c.* Pulmonary trunk in a case of tetralogy of Fallot with pulmonary valvular stenosis. Nonspecific fibrous-tissue thickening of intima. At the surface of the lesion there is a deposit of platelets, fibrin and occasional leukocytes (ELVG; × 90). *d.* Mitral valve in a case of aortic stenosis and insufficiency with bacterial endocarditis. The jet lesion on the subjacent mitral valve is infected and is composed to a large extent of colonies of bacteria (Brown Gram stain; × 140).

'onditions which may be associated with je lesions are the various kinds of valvular st osis or insufficiency, stenosis of ventricu- la outflow tracts, certain septal defects, and al ormal communications between the aorta o ts branches and a cardiac chamber, a pul- m ary artery or a vein.

Grossly, jet lesions appear as focal crops of thickenings of the endocardium or of the intima of involved blood vessels. There is a tendency, especially when the stream apparently strikes the wall obliquely, for the components of the jet lesion to have a cusplike orientation. The cusps formed are directed

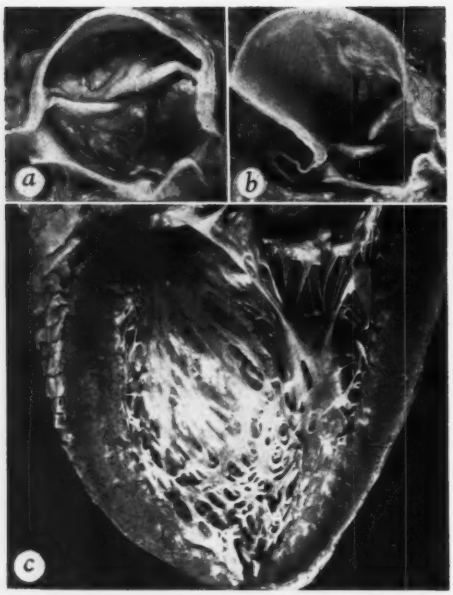

FIG. 2. Congenital bicuspid aortic valve with stenosis and insufficiency. *a*. The aortic valve from above. Congenital bicuspid valve with calcification causing irregularity responsible for both stenosis and insufficiency. *b*. Above the valve the probe points to a jet lesion on the ascending aorta (photomicrograph of this lesion appears as figure 1*b*). *c*. The left ventricle. At the apical portion there is widespread fibrous thickening of the endocardium representing jet-lesion formation from the element of insufficiency of the diseased aortic valve.

with their concavities toward the source of the jet stream. Histologically, jet lesions are composed of nonvascular fibrous tissue, mainly collagenous, although in old lesions some elastic tissue may be found as well (fig. 1*a* and *b*).

The usual absence of blood vessels in the jet lesion indicates that it appears to be a primary overgrowth of connective tissue of the lining of the involved vessel or cardiac chamber. In some instances, however, there are deposits of platelets and fibrin on the surface of the lesion suggesting that at times some of the plaque or excrescence may result from a process of organization of such surface deposition of blood elements (fig. 1*c*). There is no atheromatous material in the jet lesion, although, at times, jet lesions in arteries have

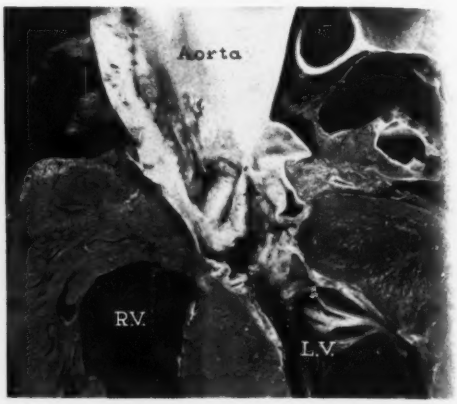

FIG. 3. Subaortic stenosis in a 14-year-old bo Aortic valve and adjacent areas. Sagittal section heart. Beneath the aortic valve (*A*), the outflo tract of the left ventricle (*LV*) shows stenosis cha acteristic of subaortic stenosis. On the aortic valv and on the ascending aorta there are jet lesions. *R* = right ventricle.

been misinterpreted as representing atheromatous plaques.

Under special circumstances wherein there is intravascular infection at the site of origin of a jet stream, bacteria may be responsible for infection of the wall of the cardiac chamber or blood vessel at the site of the impact by the jet stream. Under these circumstances, the jet lesion has a different appearance. It is represented by an accumulation of vegetations characteristic of bacterial endocarditis or endoangiitis at the site of the impact (fig. 1*d*). Depending upon circumstances, such infectious jet lesions may be primary or secondary. They are primary when, for example, the insufficiency of a valve has resulted from a bacterial infection. On the other hand, when bacterial infection complicates the existence of a stenotic or insufficient lesion, then jet lesions of the inflammatory type are secondary, being superimposed on pre-existing fibrous elevations which represent jet lesions that had developed in the stages of cardiac dysfunction before the inflammatory disease appeared.

Most of the lesions with which we are concerned resulted from purely mechanical rather than infectious factors.

Sites of Jet Lesions

Aortic Stenosis. Frequently, in aortic valvular stenosis, a jet lesion is present on the wall of the ascending aorta.

The natural direction of blood passing through the aortic valve obliquely toward the right is responsible for the fact that in many instances of aortic valvular stenosis, the jet lesion involving the ascending aorta lies along the right aspect of this structure, beginning a short distance above the aortic valve. At times the jet lesion lies upon the surface of the posterior aspect of the ascending aorta, on that part of the aorta which lies in contact with the anterior aspect of the atrial septum and the adjacent anterior walls of the atrial chamber (fig. 2). When the tendency for the stream to strike the posterior wall occurs, it is believed to result from peculiarities of the valvular disease in the particular case rather than from the primary direction of blood flow leaving the left ventricle.

Subaortic Stenosis. In subaortic stenosis, jet lesions occur not only upon the right wall of the ascending aorta but also upon the ventricular aspect of the aortic valve (fig. 3). One is led to wonder whether the valvular jet lesions in this disease result in part from the trauma of the jet stream striking the closed aortic valve in the earliest part of systole just before the aortic valve opens. After the valve opens, the jet may traumatize the wall of the ascending aorta and cause a lesion there. In addition, the hemodynamic situation exists wherein intense fluttering of the valve leaflets about the high-velocity stream might be expected.

Aortic Insufficiency. Mural jet lesions in the left ventricle are common in aortic insufficiency of various types.

When left ventricular jet lesions occur as result of incompetence of the aortic valve, whatever its cause, the lesions lie closely subjacent to the aortic valve, but they occupy a variety of foci in this region. A common site for a left ventricular jet lesion is the ventricular surface of the anterior leaflet of the mitral valve, as we have seen in some cases of congenital bicuspid aortic valve with aortic incompetence (fig. 4*a*). Another common site is the surface of ventricular septum subjacent to the aortic valve. In rheumatic aortic insufficiency, especially when associated with aortic stenosis, the tendency is great for a jet lesion to be found in this location (fig. 4*b* and *c*). We have also observed lesions in this position in syphilitic aortic insufficiency and

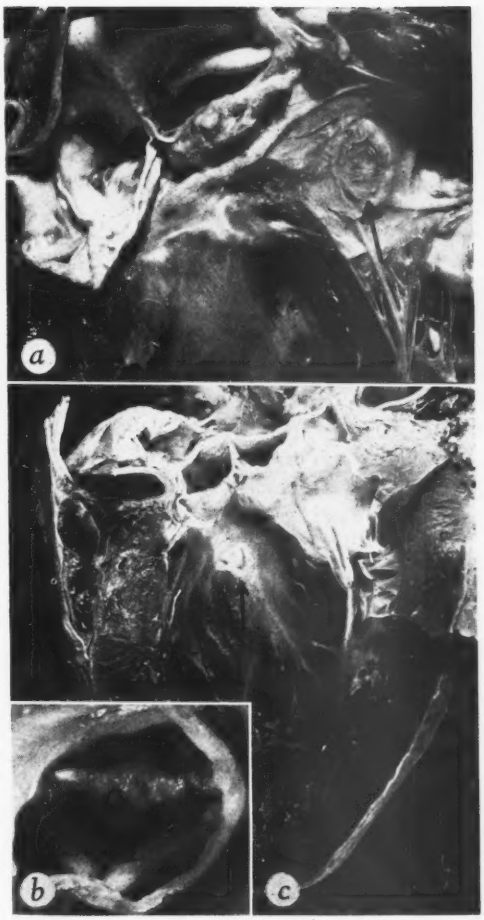

Fig. 4. Aortic insufficiency. *A.* Congenital bicuspid aortic valve in a 28-year-old man with aortic coaretation. Jet lesion is present on the ventricular surface of anterior mitral leaflet (*above point of arrow*). *b.* and *c.* A case of rheumatic aortic insufficiency in an adult. *b.* Aortic valve seen from above. In *c*, beneath the opened aortic valve, a jet lesion (*point of arrow*) is seen on the left ventricular surface of the ventricular septum.

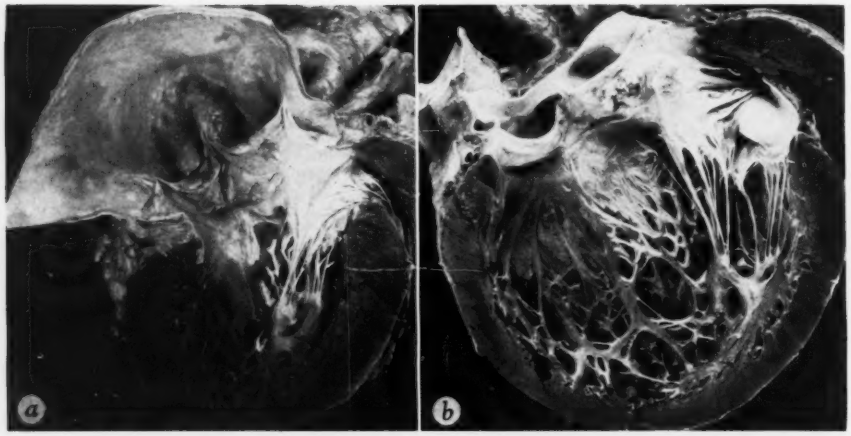

FIG. 5. *a*. Left ventricle and ascending aorta. There is senile dilatation of the aorta. A jet lesion resulting from aortic insufficiency is present on the ventricular septum immediately beneath the aortic valve. *b*. Left ventricle and aortic valve in a case of congenital bicuspid aortic valve with healed bacterial endocarditis. There is perforation of one leaflet, and jet lesions are present on the ventricular septum inferior to the perforated leaflet.

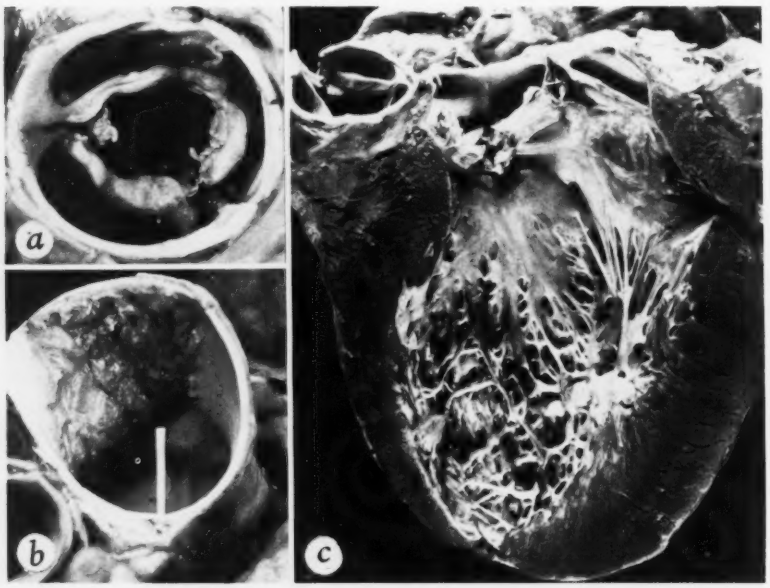

FIG. 6. Congenital aortic stenosis and insufficiency in a 16-year-old girl. *a*. The aortic valve from above, showing congenital stenosis and insufficiency. Valvulotomy had been done on this valve. *b*. Ascending aorta. A jet lesion (above probe) is seen on the right posterior lateral wall of the ascending aorta. *c*. The aortic valve and left ventricle opened. The apical half of the left ventricle shows extensive endocardial scarring representing jet-lesion formation as a result of the aortic incompetence.

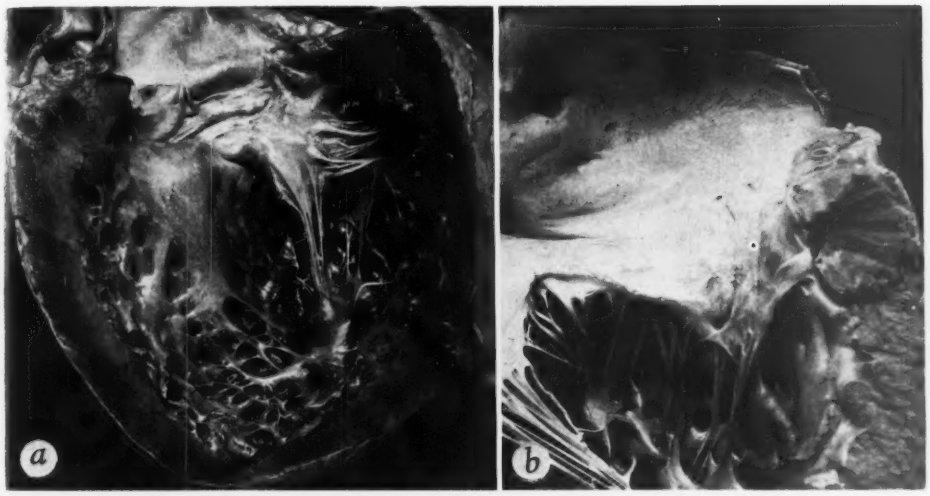

FIG. 7. Rheumatic aortic insufficiency in a young man with complicating mitral insufficiency. *a*. Aortic valve and left ventricle. There is left ventricular enlargement as a consequence of rheumatic aortic insufficiency. *b*. The mitral valve and the left atrium. The posterior leaflet of the mitral valve and the adjacent left atrial wall show jet lesions resulting from mitral insufficiency. The latter appears to have complicated the state of enlargement of the left ventricle with tension on the mitral chordae.

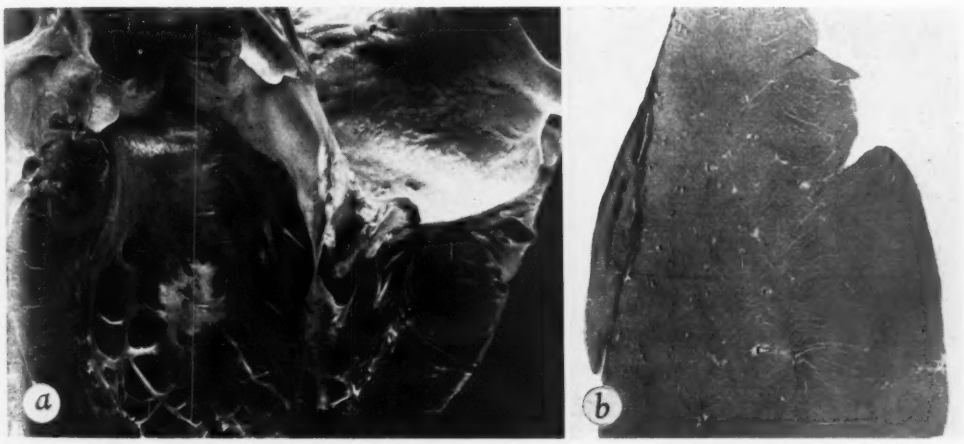

FIG. 8. Mitral stenosis with jet lesion on septal wall of left ventricle. *a*. Gross specimen in sagittal section. *b*. Photomicrograph (ELVG; × 3).

in a rare case of aortic incompetence which appeared to have resulted from senile dilatation of the aorta (fig. 5*a*).

In the relatively uncommon situations when left ventricular jet lesions occur below the upper third of the chamber, the lesions tend to be broadly distributed in contrast to the relatively confined sites of involvement seen, as a rule, in the upper third of the chamber.

In a case of congenital bicuspid aortic valve with healed bacterial endocarditis which we studied, there was a perforation in the more posterior of the two aortic cusps. The central portion of the midseptal wall of the left

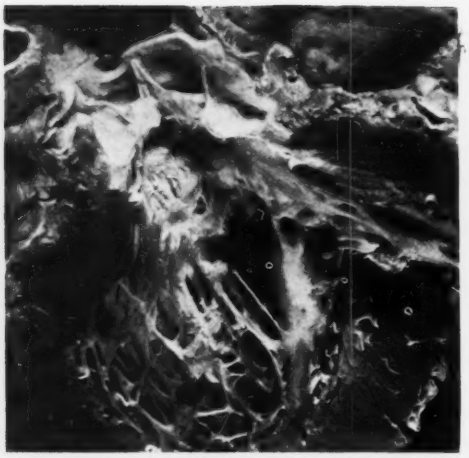

FIG. 9. Coexistent mitral stenosis and aortic insufficiency. The septal wall of the left ventricle shows two jet lesions. The first, resulting from the aortic insufficiency, lies immediately beneath the aortic valve. The second, resulting from the mitral stenosis, lies about midway between the apex and the base of the septum.

ventricle showed a large patch of fibrous thickening resulting from the aortic regurgitant stream (fig. 5*b*).

In those cases of congenital, coexisting, aortic valvular stenosis and insufficiency that we have observed, the entire lower half of the left ventricular endocardium was thickened irregularly by collagen, a process interpreted as jet-lesion formation (fig. 6). A similar process was observed in a case of congenital bicuspid aortic valve which had become involved by acquired stenosis and insufficiency. The possibility of these lesions being a focal endocardial fibroelastosis is not admitted since the tissue of the lesion is collagenous rather than containing wavy deposits of elastic tissue.

Additional mention should be made of aortic insufficiency associated with active bacterial endocarditis. Here there is a great tendency for the regurgitant streams to strike the anterior mitral valve and its attached chordae. Under these circumstances infection develops in the structures receiving the impact. Not infrequently aneurysm of the valve leaflet may occur and if the secondary inflammatory lesions are sufficiently destructive, perforation of the anterior mitral leaflet may

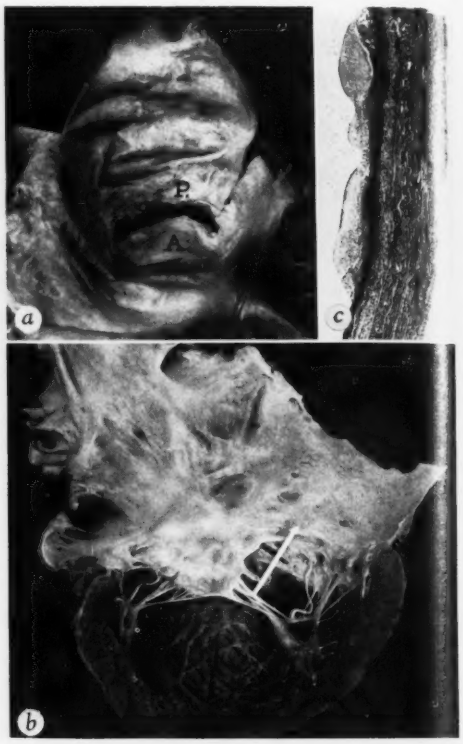

FIG. 10. Mitral insufficiency. *a*. Rheumatic mitral insufficiency. Unopened valve is viewed from above. Above the posterior leaflet (*P*) jet lesions are on the posterior wall of the left atrium. *A* = anterior mitral leaflet. *b*. and *c*. Healed bacterial endocarditis. *b*. Rupture of chordae and erosion of valvular tissue are evident in relation to the posteromedial commissure. The posterior wall of the left atrium shows an area of jet lesions (*above arrow*). *c*. Photomicrograph of jet lesions (ELVG; × 9).

follow. More commonly, however, rupture occurs in those chordae which insert into the central part of this mitral leaflet. The resulting mitral insufficiency complicates the picture, and left atrial jet lesions develop.

While mitral incompetence logically may follow the destructive complications of aortic valvular bacterial endocarditis, there is yet another circumstance in which mitral incompetence may complicate aortic insufficiency. In a case which we observed, a young man had severe pure aortic insufficiency of rheumatic origin. No jet lesions were present in the left ventricle, but such lesions were pr-

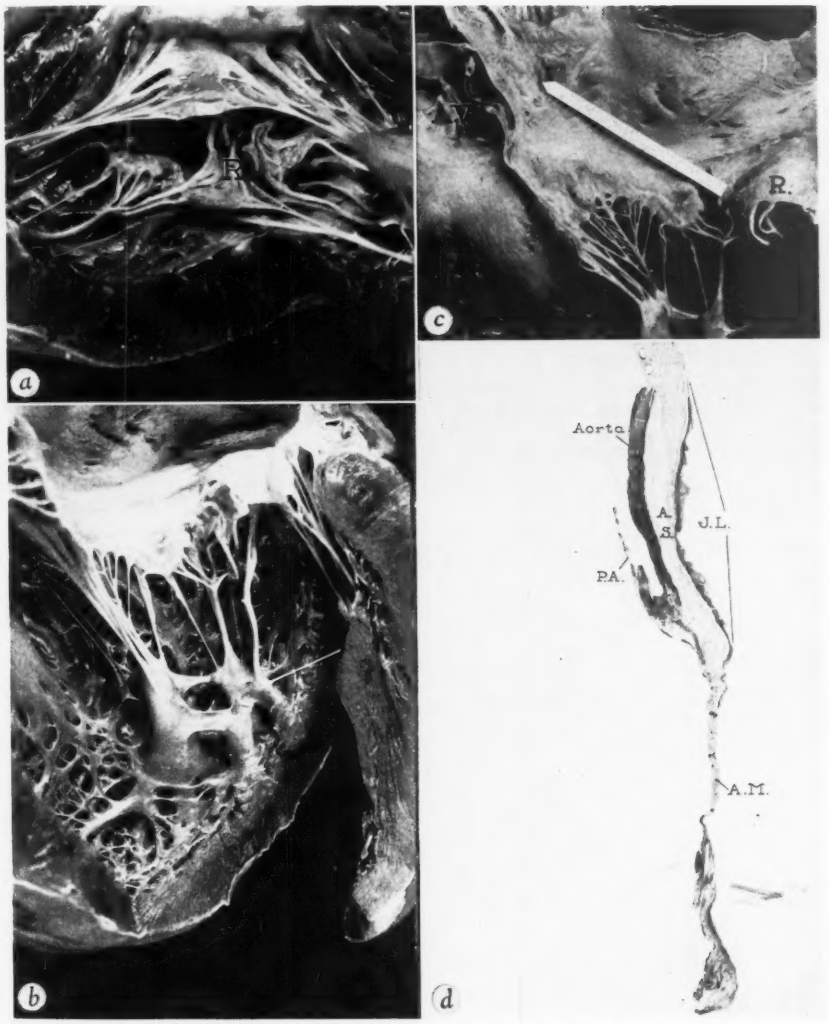

FIG. 11. Mitral insufficiency resulting from rupture of chordae attached to posterior leaflet in a 24-year-old man. *a*. Mitral valve unopened, viewed from below. Chordae to a portion of the posterior leaflet (*R*) have ruptured. *b*. Mitral valve opened. That part of the valve from which the chordae have ruptured shows a hoodlike deformity. *c*. Sagittal section of a portion of the left side of the heart. Probe shows path of regurgitant stream which had originated at the site of the ruptured chordae (*R*) and then struck the septal wall of the left atrium. The aortic valve (*AV*) lies close to the site of impact by the regurgitant stream. An artifact is seen beneath the base of the probe. *d*. Low-power photomicrograph of aortic valve, atrial septum and related structures from a case similar to that illustrated in *a*, *b* and *c*. The jet lesions (*JL*) on the atrial septum (*AS*) lie close to the posterior cusp of the aortic valve (*PA*). *AM* = anterior mitral leaflet (ELVG; × 2).

upon the atrial aspect of the posterior ral leaflet and upon the contiguous portion he left atrium (fig. 7). The mitral valve otherwise normal. The left ventricle was greatly dilated and elongated. We interpreted these changes as probably resulting primarily from the aortic insufficiency and causing undue tension upon the mitral chor-

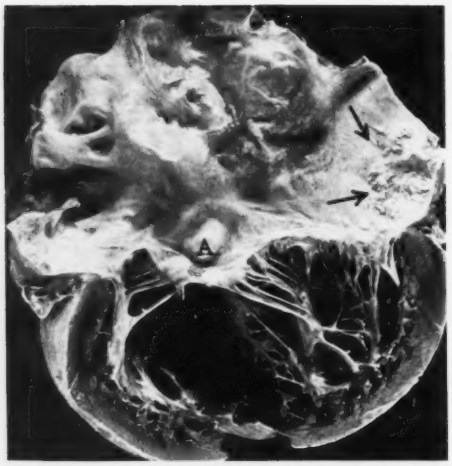

FIG. 12. Mitral insufficiency resulting from rupture of chordae attached to anterior leaflet (*A*). The jet lesions (*arrows*) lie on the posterior wall of the left atrium.

dae. The latter feature is further hypothesized to have caused improper approximation of the two mitral leaflets, and the resulting mitral insufficiency explained the presence of the jet lesions which were demonstrated.

The complex of aortic insufficiency and ventricular septal defect may yield jet lesions on the right ventricular septal endocardium just inferior to the position of the ventricular septal defect. Such lesions indicate that at least part of the regurgitant stream is directed into the right ventricle.

Mitral Stenosis. In severe mitral stenosis associated with a high left atrial pressure, it is conceivable that a jetlike stream of blood would enter the left ventricle during diastole of this chamber. That this occurs is evidenced by the fact that in an occasional case of mitral stenosis a jet lesion may be identified in the left ventricle. Such lesions may be found on the surfaces of the papillary muscles or on the ventricular septum opposite the mitral orifice (fig. 8). Our experience indicates that it is the exceptional case of mitral stenosis that exhibits such traumatic lesions in the left ventricle.

Several factors may explain the absence of left ventricular jet lesions in mitral stenosis. If the orifice is relatively large or if the left atrial pressure is not particularly high, a high-velocity stream does not exist and so no basis for unusual trauma to the left ventricular chamber is present. Another factor may be the orientation of the mitral-valve orifice. In those cases in which a jet lesion occurred on the ventricular septum, the mitral orifice was so positioned as to suggest that the blood flowed in a somewhat horizontal direction toward the septum. When jet lesions were absent, the orientation of the mitral orifice was such as to suggest that the stream of blood flowed into the left ventricle in a vertical direction toward the anatomic apex of this chamber. It is conceivable that in the latter type of case the kinetic energy of the jet stream is dissipated in the left ventricular cavity and so does not impact against the left ventricular endocardium.

Of special interest are rare cases of mitral stenosis associated with aortic stenosis and insufficiency when left ventricular jet lesions occur from involvement of both valves. In a case which we observed, there was such a lesion on the septal wall immediately below the aortic valve which we interpreted as resulting from the aortic insufficiency. Below this lesion the septal wall contained a second and distinct patch of fibrous tissue caused by the mitral stenosis (fig. 9).

Mitral Insufficiency. Mitral insufficiency of rheumatic origin is not frequently associated with distinct jet lesions in the left atrium. This may possibly be explained by the direction of the regurgitant stream into the cavity of the left atrium, wherein the energy of the stream is dissipated. In those cases of rheumatic mitral insufficiency in which jet lesions are identifiable, they usually occur on the posterior wall of the left atrium immediately above the posterior leaflet of this valve (fig. 10*a*).

Mitral insufficiency resulting from bacterial endocarditis has a varied picture. In instances in which there is excavation of tissue of either leaflet, the jet lesions appear on the posterior wall of the left atrium (fig. 10*b* and *c*). A particularly interesting group of cases consists of those in which the bacterial endocarditis is associated with ruptu

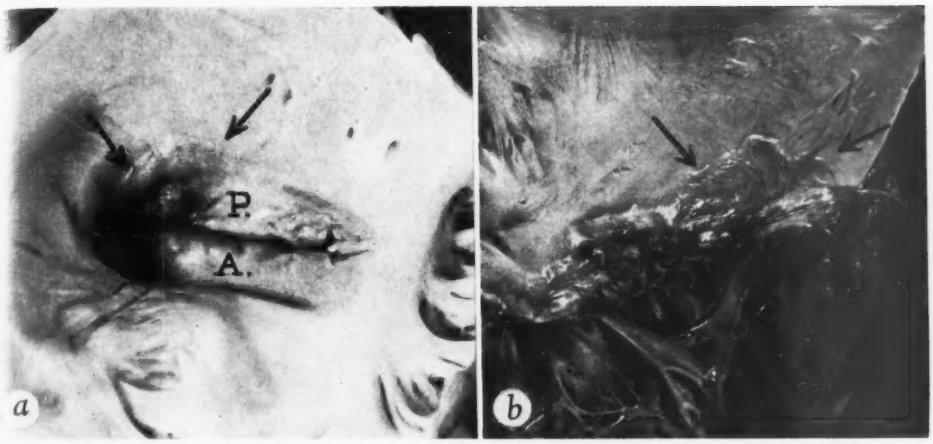

FIG. 13. Congenital mitral insufficiency in a 5-year-old child who also had a ventricular septal defect. *a*. The mitral valve is viewed from in front and above. In the posterior leaflet (*P*) there are two deficiencies. Above the larger there is a fan-shaped jet lesion (*between arrows*) on the posterior wall of the left atrium. *A* = anterior leaflet of mitral valve. *b*. The valve opened. Above the larger congenital deficiency of the posterior leaflet the jet lesion (*between arrows*) lies on the posterior wall of the left atrium.

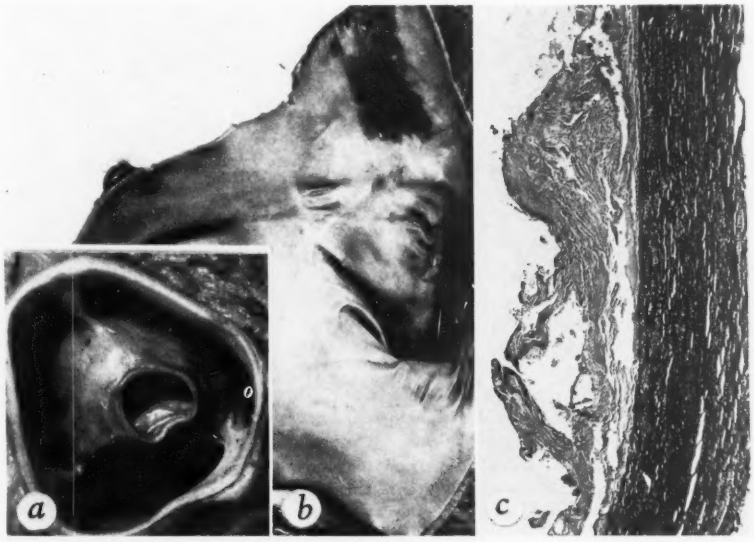

FIG. 14. Pulmonary valvular stenosis with intact ventricular septum. *a*. The unopened pulmonary valve from above. *b*. At the origin of the left pulmonary artery near the bifurcation of the pulmonary trunk (right upper portion of illustration) is an elevation of the intima which is a jet lesion. *c*. Photomicrograph of the jet lesion shown in *b* (ELVG; × 30).

of hordae. Usually, if the patient survives su an episode, the extent of ruptured chor- da is restricted to a relatively small region. Th creates a change of the valve in which, at th site of the ruptured chordae, the valve leaflet protrudes into the atrium as a hood-shaped structure. This hoodlike deformity seems to have an influence in deflecting the blood to that part of the left atrium which lies opposite the site of the ruptured chordae.

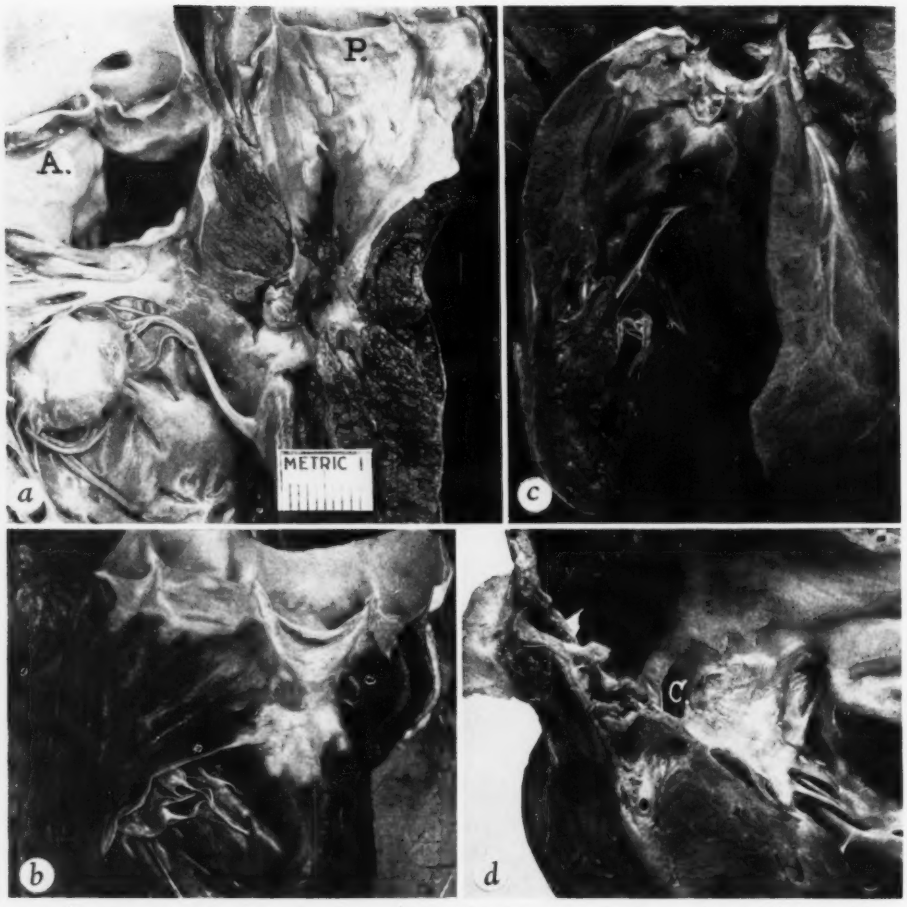

FIG. 15. *a.* Outflow tract of right ventricle and pulmonary valve in tetralogy of Fallot with severe infundibular stenosis. Above marked narrowing of the lower ostium of the infundibulum, where endocardial thickening of a considerable degree is present, there is a series of jet lesions involving the wall of the infundibulum and the adjacent leaflets of the pulmonary valve (*P*). *A* = aortic valve. *b.* Rheumatic pulmonary valvular insufficiency. Jet lesion beneath valve. From a 61-year-old man who also had involvement of the aortic and mitral valves. *c.* Pulmonary valvular insufficiency in an adult with patent ductus arteriosus and pulmonary hypertension. Jet lesion is present over a wide area immediately beneath the valve. *d.* Tricuspid insufficiency in an adult with pulmonary valvular stenosis and intact ventricular septum. A jet lesion can be seen on the septal wall of the right atrium just anterior to the ostium of the coronary sinus (*C*).

Thus, in rupture of the chordae to the posterior leaflet, the direction of the stream is forward and medially. The stream impacts against the atrial septum. In this location the lesions are removed from the base of the aorta by only a few millimeters (fig. 11). We have observed that the systolic murmur and thrill created by impingement of the regurgitant stream against the atrial septum may yield clinical signs that may mimic aortic stenosis.

When rupture of chordae involves those attached to the anterior mitral leaflet, the blood is deflected posterolaterally where it strikes the posterior wall. We observed a case in which bacterial endocarditis had

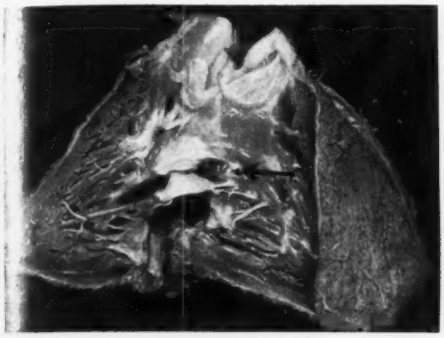

Fig. 16. Right ventricle in a case of small ventricular septal defect (*arrow*) in a 5-year-old boy. Jet lesion is on anterior wall of chamber.

started primarily on the aortic valve. This resulted in minor degrees of erosion of this valve. There was regurgitation onto the anterior mitral valve which showed a jet lesion on an unruptured aneurysm. Additionally, subjacent chordae which inserted into the central portion of the anterior leaflet had ruptured, causing the mitral valve to become incompetent. The jetlike stream from the mitral incompetence caused lesions on the posterior wall of the left atrium (fig. 12). In this patient, the systolic murmur was transmitted to the left axilla and back.

There is a large variety of congenital malformations of the mitral valve which lead to its incompetence. One of these is characterized by the presence of accessory chordae and commissures of the posterior leaflet. The deformity is responsible for inadequate apposition of one portion of the posterior leaflet upon the other with resulting incompetence through the deficiency. In such instances, the jet lesions appear directly above the deficiency in the posterior leaflet, upon the posterior left atrial wall (fig. 13).

Pulmonary and Infundibular Stenosis. Jet lesions associated with pulmonary or infundibular stenosis are most graphically observed in cases of congenital pulmonary valvular stenosis with intact ventricular septum. The jet stream strikes the top of the pulmonary arterial bifurcation or the nearby origin of the left pulmonary artery (fig. 14). In this region it is significant that the systolic murmur and thrill characteristic of this condition are often observed most intensely, not at the level of the pulmonary valve, but some distance above it.

In those cases of tetralogy of Fallot in which the major obstruction lies at the pulmonary valve, jet lesions occur on the wall of the pulmonary trunk, the exact position being determined by the orientation of the plane of the stenotic orifice.

In cases of tetralogy of Fallot wherein the major obstruction lies in the right ventricular infundibulum, lesions of the jet type are found on the ventricular face of the pulmonary valve. In particular when an infundibular chamber occurs beyond a point of severe localized infundibular stenosis, the wall of the chamber may likewise show such lesions (fig. 15).

Pulmonary Insufficiency. When pulmonary valvular insufficiency occurs, jet lesions may be found immediately inferior to the valve. Usually these lesions are represented by broad areas of relatively minor endocardial thickening (fig. 15*b* and *c*).

Tricuspid Insufficiency and Stenosis. Rheumatic involvement of the tricuspid valve usually is not associated with either right ventricular or right atrial jet lesions. This may perhaps be explained by relatively minor differences in pressure between the two chambers concerned and also by the fact that the orifice, although narrowed, is still of relatively good size.

In an occasional case in which a severe right ventricular systolic hypertension has existed, as in isolated pulmonary valvular stenosis, the tricuspid valve may be mildly incompetent. The heart in such a case may have jet lesions above the septal leaflet of the valve on the septal surface of the right atrium (fig. 15*d*).

Septal Defects. Since jet lesions depend upon high-velocity streams starting in a high-pressure source and entering a region of lower pressure, it is consistent that examples of pronounced lesions are seen in cases of small ventricular septal defect (fig. 16). The jet lesions are seen on the endocardium opposite the defect. In those hearts having the com-

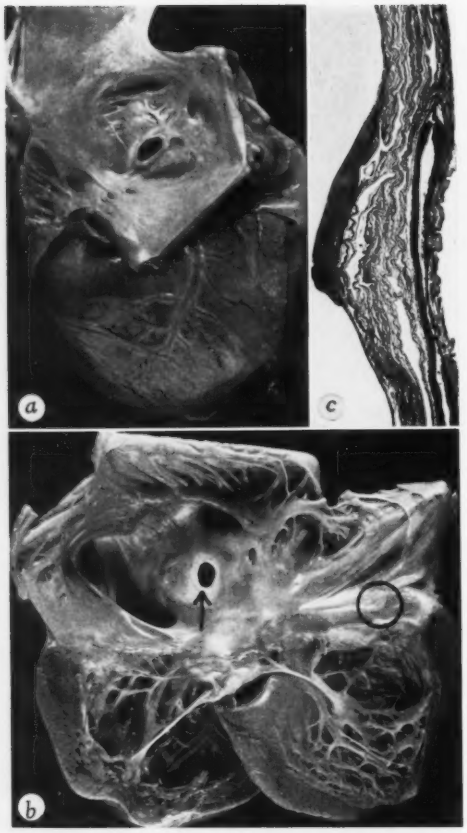

FIG. 17. Mitral atresia in a 14-year-old girl. *a.* The left atrium shows no mitral orifice. There is a small atrial septal defect. *b.* The right atrium. Opposite the small atrial septal defect the posterior wall of the right atrium shows a jet lesion (*circle*). *c.* Photomicrograph of the jet lesion of the right atrium (ELVG; × 10).

mon variety of defect, the anterior wall of the right ventricle near the tricuspid attachment is characteristically involved. In addition, the septal leaflet of the tricuspid valve, which at times overhangs the defect, is also frequently distorted by such lesions.

In the hearts of patients with large ventricular septal defects in whom the left and right ventricular pressures were about equal during life, there are no well-developed jet lesions.

In the hearts of patients having atrial septal defect as an isolated lesion, no jet lesions are identifiable in the right atrium even though large volumes of blood enter this chamber. Recalling that the defect is usually large and that the pressure differences between the two atria are negligible makes absence of jet lesions in this condition understandable and, indeed, predictable.

We have observed a right atrial jet lesion in a heart having a small atrial septal defect in association with mitral atresia (fig. 17). In this condition the small atrial septal defect was the only effective outlet for the left atrium, which had received all the pulmonary venous blood. Though physiologic measurements had not been made, it is assumed that the left atrial pressure was elevated and a high-velocity jetlike stream of blood flowed through the small atrial septal defect. Jet lesions were present upon the posterolateral wall of the right atrium opposite the small atrial septal defect.

Communication Between the Aorta and a Cardiac or a Pulmonary Vessel. In hearts having a ruptured aortic sinus aneurysm, when the history indicates that the patient had lived for some time with it, jet lesions exist in that right-sided chamber into which the rupture of the aneurysm occurred. In one of the cases we observed in which the aneurysm had ruptured into the right ventricular outflow tract and there was an associated ventricular septal defect, jet lesions had developed upon the anterior wall of the outflow tract of the right ventricle.

In another case, an aortic sinus aneurysm had ruptured, 2 years before the patient's death, through the lower part of the septal wall of the right atrium into the right atrial cavity. Jet lesions of well-defined nature were present on the posterolateral aspect of the right atrium, opposite the site of the rupture in the aneurysm (fig. 18).

The vessels in a classic patent ductus arteriosus often show focal endarteritis characteristic of the jet lesion in the pulmonary artery opposite or proximal to the pulmonary orifice of the ductus. Such lesions occur either in the left pulmonary artery or in the pulmonary trunk itself (fig. 19). The position of

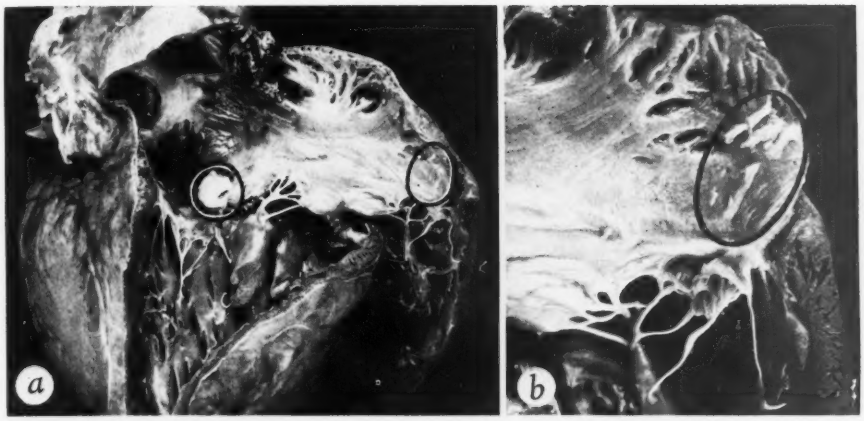

FIG. 18. *a.* Ruptured aortic sinus aneurysm presenting in right atrium (*left circle*). The opposite posterior wall of the right atrium shows a collection of jet lesions (*right circle*). *b.* Close-up view of jet lesions of right atrium. From a 42-year-old woman.

the jet lesion proximal to the pulmonary orifice of the ductus correlates well with the oblique position of the ductus in which the pulmonary orifice lies in a more medial position than the aortic orifice. A jet stream coming from a ductus would therefore be expected to strike the pulmonary arterial wall in a proximal location.

The counterpart of the jet lesions resulting from persistent patency of the ductus is seen in the great vessels of patients who have had a Blalock-Taussig anastomosis between the left subclavian and left pulmonary arteries. In one case in which the operation had been done on the left side, the direction of the anastomotic segment of the left subclavian artery was such that its aortic origin was more medial than its left pulmonary arterial connection. It is a reasonable conjecture that the blood stream was directed downward and laterally to account for the jet lesions that were found on the inferior wall of the left pulmonary artery distal to the site of anastomosis.

Coarctation of the Aorta. Beyond the region of aortic constriction in coarctation of the aorta, jet lesions may be present but are not universally found. When present, they tend to lie on the inferior wall of the aorta within a centimeter of the constriction. The presence of jet lesions in this location is readily understood as a reaction to a high-velocity stream originating at the narrowed point in the aorta. Absence of a jet lesion is probably to be explained by peculiar orientation at the obstruction as a result of which the jet is directed toward the center of the aortic lumen and the kinetic energy is dissipated within the aortic lumen.

FIG. 19. Patent ductus arteriosus with infected jet lesion (*arrow*) near the pulmonary valve (*P*). *D* = patent ductus arteriosus; *A* = aorta. From a 14-year-old girl. Specimen contributed by Dr. James H. Peers.

Summary

High-velocity streams (jets) of blood are a hemodynamic characteristic when a high-pressure gradient exists across a small orifice. If such jet streams strike the wall of the receiving compartment, be it either cardiac chamber or blood vessel, the focal trauma causes a fibrous reaction designated herein as a jet lesion. At the site of impact where jet lesions are formed, the jet stream is either arrested or deflected and imparts energy to the area which may vibrate and give rise to an audible murmur. Jet lesions may be considered as designating possible sites of origin of murmurs in whole or in part, and in this regard may be utilized in the explanation of the particular positions of the maximal intensity of murmurs recorded during life. Random examples in support of this proposition are the systolic murmurs heard at maximal intensity in the left subclavicular area in some patients with congenital pulmonary valvular stenosis; in the left scapular area in patients with mitral regurgitation in which it is believed the anterior leaflet was of inadequate length to meet the posterior leaflet; and in the aortic area in patients with mitral regurgitation resulting from rupture of the chordae to the posterior leaflet which then behaves as a hood-like baffle directing the regurgitant stream forward and to the right.

Summario in Interlingua

Currentes de sanguine de alte velocitate ("rapidos") es un characteristica hemodynamic que occurre quando un gradiente de alte pression existe a transverso un micre orificio. Si un tal rapido batte contra le pariete del compartimento receptori (que pote esser un camera del corde o un vaso de sanguine), le trauma local causa un reaction fibrose que es designate in le presente reporto como "lesion rapidal." Al sito de impacto ubi le lesion rapidal es formate, le rapido es arrestate o illo es deflectite e imparti energia al area circumjacente que pote vibrar e producer assi un murmure audibile. Lesiones rapidal pote esser considerate como indicatores de sitos possibile de murmures, in toto o in parte, e in iste respecto illos pote esser utilisate in le explication del positiones particular del intensitate maximal de murmures que es registrate durante le vita del patiente. Exemplos—intensitate non systematicamente—que supporta iste proposition es le murmures systolic que se audi a intensitate maximal in le area sinistro-subclavicular in certe patientes con congenite stenosis del valvula pulmonar; in le area sinistro-scapular in patientes con regurgitation mitral (ubi le supposition ese que le cuspide anterior es inadequamente longe pro junger se con le cuspide posterior); e in le area aortic in patientes con regurgitation mitral como resultato de ruptura del chordas del cuspide posterior que alora age como un deflector que dirige le currente del regurgitation in un direction antero-dextrorse.

References

1. Zahn, F. W.: Ueber einige anastomische Kennzeichen der Herzklappeninsufficienzen. Verhandlungen des Congresses für innere Medicin. **13**: 351, 1895.
2. Saphir, O.: Endocardial pockets. Am. J. Path. **6**: 733, 1930.
3. —: Anatomic evidence of functional disorders of the heart. Arch. Path. **16**: 315, 1933.
4. Ingham, D. W., and Henthorne, J. C.: Endocardial pockets. Arch. Path. **25**: 250, 1938.
5. Gouley, B. A.: The aortic valvular lesion associated with the Austin Flint murmur. Am. Heart J. **22**: 208, 1941.

The Hemodynamic Effects of Quantitatively Varied Mitral and Aortic Regurgitation

By Stanley J. Sarnoff, M.D.

The material of this presentation has been published in Circulation Research **5**: 539, 546, 1957.

Radiologic Technic for Qualitative and Quantitative Study of Blood Flow

By CHARLES T. DOTTER, M.D., AND LOUIS H. FRISCHE, M.D.

RADIOLOGY is the only practical means of directly visualizing the motion of blood within the cardiovascular system of intact subjects. It not only makes possible the direct determination of the instantaneous velocity and volume of blood flow, but also allows the demonstration and localization of abnormal intravascular turbulence generally accepted as the source of heart murmurs. In radiologic visualization, a direct and highly informative approach to hemodynamics appears to have been overlooked in favor of more elaborate but less direct, reliable or productive technics such as ballistocardiography, phonocardiography and vectorcardiography. Does the aeronautical engineer confine his attention to listening to the outside of the wind tunnel? The question is purely rhetorical.

LAMINAR AND TURBULENT FLOW—BASIC CONSIDERATIONS[1]

Fluids in motion may be said to exhibit laminar or streamline flow when all component motion is unidirectional. Disregarding static factors, the energy loss in laminar flow is mainly determined by friction, which in turn is related to the viscosity of the fluid and the characteristics of the system through which it moves. Frictional energy-loss occurs mainly between layers of fluid near the periphery of the stream since the layer in contact with the containing wall is theoretically stationary. The velocity contour of such a stream is parabolic in shape. Maximum velocity occurs in midstream and amounts to twice the mean velocity.

Turbulent flow, on the other hand, involves multidirectional movement at different points within the stream. The net effect of factors which determine the character of flow is conventionally represented by Reynolds numbers —a dimensionless expression—the value of which varies *directly* with the size of conduit, the density and mean velocity of the fluid, and *indirectly* with the viscosity. Turbulent flow usually occurs when the Reynolds number exceeds 2,000.

In the cardiovascular system, turbulent flow favors efficient mixing; laminar flow favors the transportation of blood. Although perhaps all murmurs are due to turbulence, the converse is not true, judging from the combined evidence of contrast visualization and intracardiac phonocardiography. Theoretically, the murmur implies inefficiency since the production of sound wastes a finite though small amount of the heart's labor.

Unlike a glass circulatory model, the cardiovascular system does not lend itself to mathematical analysis of isolated factors governing fluids in motion. Though basic hydrodynamic principles certainly apply to the circulatory system, the modifying influence of elasticity, compliance and contractility of blood vessels is difficult to assess and even harder to control.[2, 3] Additional complications are introduced by the fact that blood flow is neither steady nor uniform. Indeed, the cyclic variation in the intensity of a murmur is but the audible manifestation of a continuously rising and falling Reynolds number!

The approach described in this report suggests that it is feasible to obtain fairly accurate cyclic curves expressing the velocity of blood and the caliber of the vessels through

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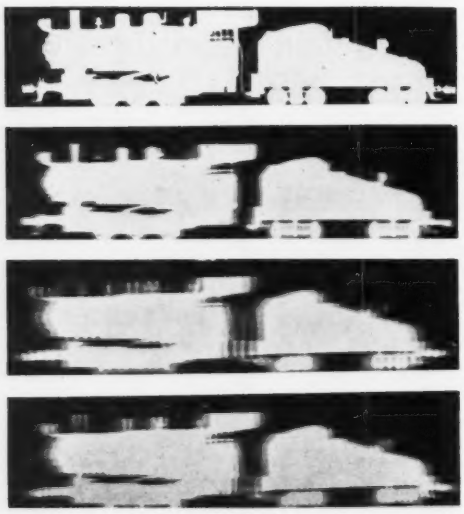


FIG. 1. Railroad model. *Upper illustration*, stationary. *Lower illustrations* are 1/30 second (four impulse) radiographs showing velocities of 36 cm. per second, 90 cm. per second, and 72 cm. per second.

which it flows. Since the density and viscosity of blood would not be likely to change during the period of observation, it follows that in various locations Reynolds numbers might be derived as a nearly continuous function of the heart beat.

MULTIPLE EXPOSURE TECHNICS FOR RADIOLOGIC STUDY OF INTRAVASCULAR MOTION

Multiple exposure photographic technics have been used successfully for tracking satellites, advertising girdles and determining blood velocity.[4] However, the cardiovascular application is unavoidably limited, being confined to photographically accessible structures (superficial capillaries) or highly artificial experimental situations (circulation models, bubble flowmeters, etc.). Radiology overcomes the limitations through its ability to record pictorially the changes in position—and thereby the velocity, acceleration, deceleration and path of motion—of objects deep within the intact circulatory system.[5]

The basic principle is exceedingly simple. *When two x-ray exposures of a moving object are cast on the same film and the intervening time is known, the distance between the resultant double-image permits calculation of the object's velocity.* Controlled experiments using objects moving at known velocities and rates of acceleration or deceleration have shown the reliability and limitations of this method of study (fig. 1).

Each year literally thousands of chance-begotten motion studies slip unnoticed past the sharpest eyes in clinical medicine, those of radiologists (!). Seemingly single the routine x-ray exposure actually consists of a series of evenly-spaced bursts which are ordinarily superimposed to cause only one image on the film. Since the time interval between these impulses is exactly 1/120 second it is possible to determine velocity of an object during an x-ray exposure by observing the distance between successive images. Typical examples of fortuitous velocity determinations are shown in figure 2.

Since one radiograph provides a two-dimensional record of three-dimensional objects, it follows that velocity cannot be measured without making allowances for movement toward or away from the x-ray tube. Simultaneous filming in two different planes is desirable in order to obtain empirical data concerning this variable.

In addition to facts about velocity, pictures can give information concerning the direction or path of motion. Night, "time-exposure" photography provides familiar illustrations of the basic principle (for example, in the streaks caused by moving headlights or the pattern of bursting fireworks). In a similar manner, radiographs can be used to study turbulent motion. The streaked images of moving radiopaque objects demonstrate the paths of their movement. Where high velocities are involved, the images of test objects will tend to be "over-extended" or blurred and thus harder to see. *In order that the radiographic appraisal of velocity as well as direction of flow be made at the same time and with maximum precision, it is desirable to employ very short, pulsed, multiple exposures of known duration and frequency.* The shorter these exposures, the sharper the resultant images; the briefer the pulse-to-pulse

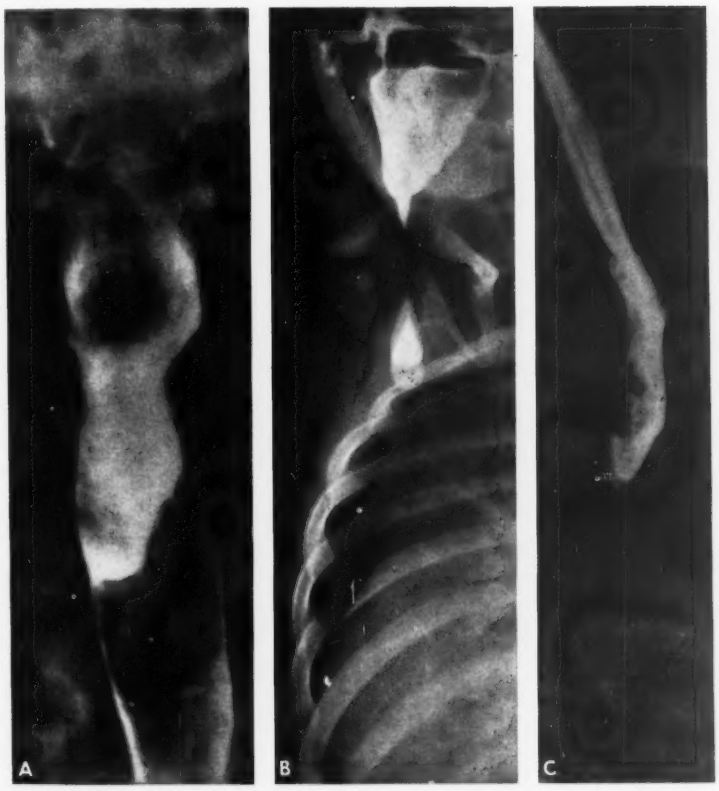


FIG. 2. Motion studies encountered in clinical radiology. *A*. Barium bolus in esophagus, showing quadruple wave-front. Progressively increasing distance between image-pairs indicates positive acceleration. *B*. Falling drop of Lipiodol. Double image indicates 1/60 second exposure. *C*. Angiocardiographic film, showing two images at leading edge of contrast medium (1/60 second exposure).

interval, the faster the motion which can be studied. It seems unlikely that movement "in depth" will prevent the study of flow-patterns, though it complicates the task.

In short, it is clear that radiology offers promising means for the study of the two major hemodynamic parameters, velocity and direction of flow. There is no doubt that radiologic study of these parameters may be applied to blood in motion, since we have done so repeatedly. Over three thousand radiographs were exposed in studying motion and evaluating various contrast agents for this purpose. The comments which follow are based on experimental data and practical experience.

SPECIAL CONTRAST AGENTS

Conventional methods of angiocardiography have proved highly useful in the delineation of gross anatomic structures and have been helpful in determining mean circulation times. Unfortunately, however, the contrast agents now in general use are far from satisfactory. Because of them, angiocardiography is an unpleasant experience to the patient and is not without risk. Heretofore, the procedure has involved the exclusive use of organic iodine-containing molecules in water solutions, several of which are commercially available. Due to their high miscibility, particularly in the presence of motion, these preparations fail to provide an adequate interface with sur-

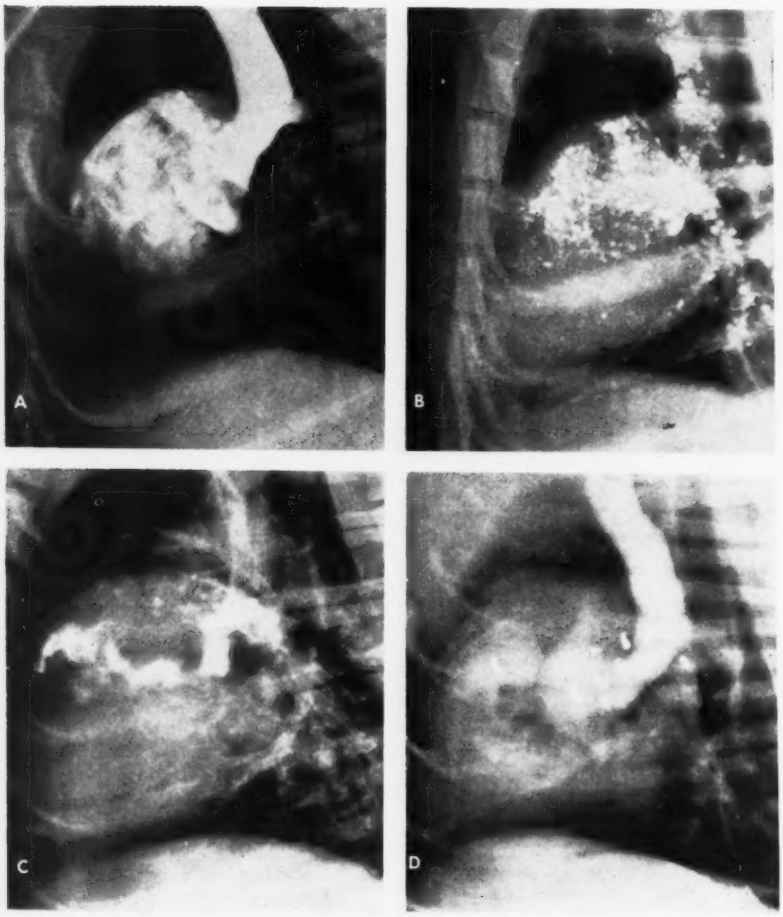


FIG. 3. Various contrast media in right-heart of dog during angiocardiography. *A*. Urokon Sodium 70 per cent, aqueous solution. Intra-atrial turbulence is evident. *B*. Lipiodol droplets. *C*. Mallinckrodt MIV-311BL (high-viscosity Urokon preparation). Laminar flow in pulmonary arteries clearly demonstrated. *D*. Mallinckrodt MM-27 (2 mm. solid pellets of Urokon 80 per cent and Dextrin 20 per cent, suspended in aqueous solution of 20 per cent Urokon).

rounding blood. They consequently cannot serve as reference points for the radiographic study of blood velocity, a problem best solved through the use of contrast media producing multiple small, discrete, punctate or particulate areas of intravascular radiopacity.

When high-viscosity solutions are employed as an alternate approach, useful information can be obtained about flow patterns within the right atrium and its tributaries. Thereafter, turbulent mixing during right ventricular filling defeats the purpose. Striking exceptions were noted in the Mallinckrodt MIV series (high viscosity preparations of Urokon Sodium), some of which were clearly capable of demonstrating laminar flow in the pulmonary arteries of the dog. Contrast agents the properties of which we have studied in dogs, are presented in table 1. Figure 3 shows the appearance of several types of media.

It is not within the scope of this discussion to cover fully the many problems which re-

TABLE —*Partial List of Contrast Media Tested for plicability to Motion Studies In Dogs*

	Agents	Remarks
Comm	ially available	
Dio	st, Hypaque,	Watery, organic iodine-containing intravascular agents used in various concentrations.
M	con,	
Ren	afin, Urokon	
S	ium	
Eth	iol	Viscid, bronchographic agent.
Lip	iol	Oily, bronchographic agent.
Iod	loral	Oily, bronchographic agent.
Sal	s	Viscid, Urokon Sodium preparation for hysterography.
Diomosil, aqueous		Watery, bronchographic agent.
Diomosil, oily		Oily, bronchographic agent.
Thorotrast		Watery, thorium dioxide (26%).
For investigational use only		
MIV-302, MIV-308BL, MIV-309BL, MIV-310-BL, MIV-311BL		High viscosity, Urokon Sodium preparations.
MIS-224		Diethyl ether, Urokon Sodium suspension.
MM-26		1 mm. pellets, Urokon Sodium and Dextrose.
MM-27		2 mm. pellets, Urokon Sodium and Dextrose.
Miscellaneous		
Air		
Carbon dioxide		
Lead EDTA		
Sugar pellets in Urokon Sodium		

mai to be solved before the ideal agent becom s available. However, certain desirable cha teristics can be stated. A particulate con ast agent should, when injected into the blo stream, produce small (0.25 to 1.0 mm.) dis te spots of radiopacity on an appropriate exposed x-ray film. These spots must be fficiently radiopaque to be perceptible on mu ple-impulse radiographs made while the pa les are moving at a rate equal to peak art ial velocities. Intravenously injected in useful amounts, a satisfactory agent should be at least as safe as the conventional media (actually there is reason to believe they might be considerably safer).

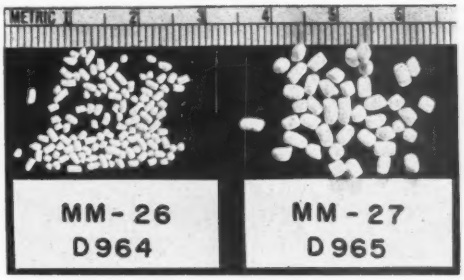


FIG. 4. Cylindroid pellets of Urokon Sodium (80 per cent) and Dextrin (20 per cent).

Theoretically, the desired particles could be bubbles of gas, drops of fluid or small solid masses. Our experience indicates that bubbles of gas are unsuitable, even when surrounded by a bolus of radiopaque fluid, due to insufficient radiographic contrast. Unusually high kilovoltage x-rays might improve this, but more proximate possibilities exist. It has been said that nongaseous agents capable of producing punctate opacification would probably produce death due to embolization. That this is not true has been repeatedly demonstrated in connection with the use of the most promising of the substances tested to date, small solid cylindroid pellets composed of Urokon Sodium (80 per cent) and Dextrin (20 per cent) (fig. 4).

The Mallinckrodt Chemical Works has provided a number of contrast substances for testing, and has also generously given advice on chemical subjects. The solid particles discussed here are designated products MM-26 and MM-27 of the Mallinckrodt Research Laboratories. Inasmuch as these particles have provided a useful approach to experimental hemodynamics, improved versions are being sought. The principal objectionable feature of the present pellets is not, as one might first assume, their embolic potential. Several hundred have been injected (up to 100 at once) into each of several medium-sized dogs without observed acute or chronic effects. These

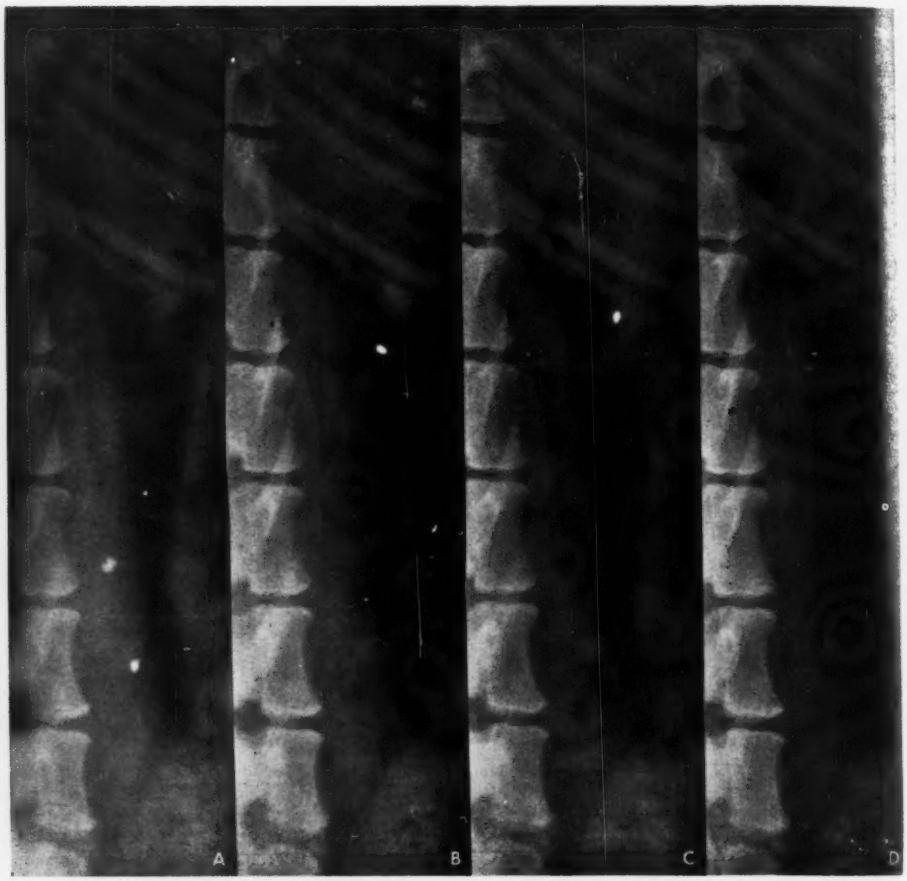


FIG. 5. Solid pellets (MM-27) in inferior vena cava of dog. *A*. Lowermost pellet presents two partially superimposed images. Images of other pellet, moving at a different velocity and/or in a different plane, barely overlap. *B*. Exposure 0.5 second later shows cephalad pellet to be moving rapidly; caudad pellet has become adherent to wall of inferior vena cava. *C*. Foremost pellet lost to view 1.5 seconds later. Caudad pellet remains adherent to wall of inferior vena cava. *D*. Previously adherent pellet no longer present, 3 minutes after first film.

particles have been so contrived as to dissolve in blood within a few seconds' time. Serial angiocardiographic studies reveal that some of the injected pellets immediately pass through the heart, are arrested in medium sized pulmonary arteries and become invisible in from 10 seconds to 2 minutes. Other injected pellets appear to become trapped in the right auricular appendage, while surprisingly, some appear to adhere to the walls of veins leading to the right atrium. In any event, all have disappeared completely, promptly and without ill effect. Their apparent tendency to adhere to vascular walls is an interesting phenomenon as well as a technical problem. Figure 5, consisting of views selected from a dog study, illustrates pellet adhesiveness and dissolution-time, as well as the determination of velocity in the inferior vena cava (*a*) at one time in two places and, (*b*) at a later time and a third place.

Another promising approach to the prob-

FIG. 6. Radiographic study of turbulence in lucite model. Particles of barium carbonate suspended in SAE-10W motor oil, forced through cavity with syringe and interconnecting rubber tubing.

lem of spot-opacification lies in the use of suspensions or solutions of radiopaque agents in droplets of relatively immiscible fluids. Initially it was hoped that diethyl ether would provide an ideal solvent for this purpose. Cinefluorographic studies were done during the first trial injection of such a suspension (MD-224, Mallinckrodt). The dog died immediately since, as the movies later showed, the ether had promptly turned into a gas as it left the catheter. To our embarrassment, we learned that the boiling point of ether is 34.5 C. Methyl-propyl ether has been tested for toxicity in the experimental animal and may offer a satisfactory substitute since its boiling point is higher than normal body temperature. However, many problems must be overcome before the achievement of a satisfactory suspension of radiopaque agent within a safe but relatively immiscible fluid.

With respect to the work under discussion, it is necessary to comment upon an important aspect of radiographic technic. Utilizing conventional x-ray circuitry and dogs as experi-

FIG. 7. Turbulence demonstrated in lucite model, using MM-27 solid pellets.

mental animals, we have been able to make satisfactory double-impulse observations of 1 to 2 mm. pellets moving in the inferior vena cava at velocities of approximately 75 to 100 cm. per second. Unfortunately, the image has usually been "blurred" due to long pulse-duration. To help solve this problem a Machlett Dynapulse high-tension switching system was developed.* This unit provides exposures of from 1 to 5 msec. duration at up to 1000 ma. tube current and 100 KV.[6] Circuitry is being added to provide multiple pulses separated by known intervals in the order of 1 msec.

Available knowledge concerning velocity of arterial blood flow plus practical experience have aided in establishing the requisite duration of exposure and the necessary interval between impulses. The maximum blood velocity to be found is probably that which occurs in pure valvular pulmonary stenosis. In this condition, despite the usual prolongation of systole, blood must pass through the narrowed

*This prototype Dynapulse unit now in operation at the University of Oregon Medical School was made available to the Minthorn Laboratory for Cardiovascular Research through the generosity of the Machlett Laboratories, Inc., Mr. John Stevenson, President.

orifices truly remarkable velocities in order to maintain a cardiac output consistent with life. That such velocities exceed 500 cm. per second is indicated by simple calculations based upon known orifices and outputs in this condition. Published experimental observations appear to confirm the calculations.[7] Since 1/120 second exposure-duration has been known to be sufficient for determination of a velocity close to 100 cm. per second, a 1 msec. exposure should suffice for the highest blood velocity likely to be encountered.

Discussion

It is hoped that further development of the basic approach described here will result in a new tool for research and teaching in cardiovascular physiology. Clinical applications have not been explored completely, nor could they be for a matter of years. Even though the determination of absolute blood velocity and flow-volume were to fall short of present expectations, *relative* observations would be clinically useful. For example, knowledge of the proportionate amount of blood flowing to the various lobes of both lungs could aid in determining the need for and scope of resectional surgery. Relative pulmonary arterial velocities may provide a means for the differential diagnosis of a number of conditions affecting the pulmonary vascular tree—and there are many of these. The determination of the curve of myocardial power output, a possible outcome of this work, would have considerable impact on clinical cardiology. One of this work's more dramatic applications would lie in the clinical appraisal of turbulence. For all practical purposes, murmurs are the audible manifestations of turbulent blood flow. Our own experiments with models, such as that shown in figures 6 and 7, indicate that radiologically recognizable changes in flow pattern occur with or before an audible murmur whenever factors favoring turbulence are increased. It is possible, therefore, that the proposed approach could significantly expand the information provided by auscultation. Unlike the stethescope, the radiograph would provide a permanent record of the site of origin of murmurs as well as the direct cause. Clinical terms, such as "functional murmurs," could happily be discarded in favor of precise knowledge as to the genesis of the sound in question.

Summary

This preliminary report deals with the direct radiographic study of discrete, relatively small spots of artificial radiopacity during their passage through the cardiovascular structures and offers a new and promising technic for studying the motion of blood. As used here, motion refers to movement of and within the blood stream. So defined, it is fundamental to the subject-matter of hemodynamics. Continuing studies are focused upon two major hemodynamic parameters: 1. *The velocity, acceleration and deceleration of circulating blood.* Through appropriate specialized radiographic technics, it is possible to measure the movement of blood as a function of time. Observations may be completed in 1 msec., repeated in rapid sequence and made simultaneously at many different points within the cardiovascular system. 2. *Flow characteristics of circulating blood.* The graphic study of flow patterns at multiple points within the blood stream can be carried out simultaneously with blood velocity observations. By analogy, in this technic the blood vessels and chambers of the heart serve as wind tunnels; the blood is the wind, the spots of opacity are smoke tracers and the myocardium is the source of power.

The results of extensive experimental studies indicate that the above goals are achievable and warrant the considerable effort and costs involved. It is hoped that this preliminary report will encourage others to explore the possibilities of the method and thereby hasten its perfection.

Summario in Interlingua

Isto es un reporto preliminari que tracta del directe studio radiographic de discrete e comparativemente micre areas de radio-opacitate artificial durante lor passage a transverso le structuras cardiovascular. Le reporto pre-

senta un nove e promittente methodo pro le studio del motion del sanguine. Le termino 'motion' es usate hic pro designar un movimento del sanguine e intra le sanguine. In iste senso, le termino es de importantia fundamental pro le thematica del studio hemodynamic. Studios nunc in progresso se occupa de duo complexos major del hemodynamica. *(1) Le velocitate, acceleration, e deceleration del sanguine circulante.* per le uso de appropriate technicas radiographic specialiste, il es possibile mesurar le movimento del sanguine como function del tempore. Le observationes pote esser completate in 1 msec, repetite in un sequentia rapide, e facite simultaneemente a multe differente punctos intra le systema cardiovascular. *(2) Characteristicas del fluxo del sanguine circulante.* Le studio graphic del conditiones de fluxo a multiple punctos intra le currente de sanguine pote esser effectuate simultaneemente con observationes del velocitate del sanguine. A parlar analogicamente, in iste methodologia le vasos de sanguine e le cameras del corde es un tunnel aerodynamic: le sanguine es le aere (i.e. le vento), le areas de radio-opacitate es traciatores-fumo, e le myocardio es le fonte de energia.

Le resultatos de extense studios experimental indica que le supra-signalate objectivos pote esser attingite e que le costo e le effortio (le quales es considerabile) non es guastate. Es exprimite le spero que le presente reporto preliminari va incoragiar alteros e explorar le possibilitates del methodo e a accelerar [illegible]si su perfection.

REFERENCES

1. Schoder, E. W.: Hydraulics. *In* Section 3: Mechanics of Solids and Liquids of *Mechanical Engineers' Handbook* (Edited by Lionel S. Marks). Ed. 4., New York, McGraw-Hill Book Co., Inc., 1941.
2. Gidlund, Å.: Development of apparatus and methods for roentgen studies in haemodynamics. Acta Radiol. Suppl. **139**: Stockholm, 1956.
3. Kjellberg, S. R.: Die Mischungs- und Strömungs-verhältnisse von Wasserlöslichen Kontrastmitteln bei Gefäss- und Herzuntersuchungen. Acta Radiol. **24**: 433, 1943.
4. McDonald, D. A.: The velocity of blood flow in the rabbit aorta studied with high-speed cinematography. J. Physiol. **118**: 328, 1952. —: The occurrence of turbulent flow in the rabbit aorta. J. Physiol. **118**: 340, 1952.
5. Dotter, C.: Motion in cardiovascular radiography. Circulation **12**: 1034, 1955.
6. —, and Rogers, T. H.: High tension switch tube for roentgenography. Am. J. Roentgenol., Rad. Ther. and Nuc. Med. **75**: 83, 1956.
7. German, W. J., and Black, S. P. W.: Intra-aneurysmal hemodynamics—Jet action. Circulation Research **3**: 463, 1955.

Origin of Heart Sounds as Elucidated by Analysis of the Sequence of Cardiodynamic Events

By EUGENE BRAUNWALD, M.D., AND ANDREW G. MORROW, M.D., F.A.C.S.

The genesis of the first heart sound has been the subject of considerable speculation because of its simultaneity both with mitral valve closure and with the onset of left ventricular contraction. In the presence of mitral stenosis, however, it has been pointed out that the presence of a pressure gradient between the left atrium and left ventricle at the end of diastole results in temporal dissociation of the onset of left ventricular contraction and mitral valve closure.[1] The latter event cannot take place until the left ventricular pressure reaches the level of the elevated left atrial pressure. The time interval between the onset of left ventricular contraction and of mitral valve closure ranged from .01 to .04 seconds in 7 patients with mitral stenosis.[2] This finding was of interest in light of the phonocardiographic observations on patients with mitral stenosis which demonstrated that the first heart sound was delayed by similar intervals when it was related to the electrocardiogram.[3-5] Further, it was found that the duration of diastole was inversely related to the end-diastolic left atrioventricular pressure gradient,[1] but was directly related to the rate of pressure rise during the subsequent ventricular contraction.[2] Similarly, the time interval between the onset of ventricular depolarization and the first heart sound in patients with mitral stenosis has been noted to be inversely related to the duration of the preceding diastole,[3, 4] While such observations suggested that the first heart sound results from mitral valve closure, not from ventricular contraction,[5] conclusive evidence for this would require the simultaneous recording of heart sounds with left atrial and left ventricular pressure pulses.

Left heart pressures were recorded by means of transbronchial left heart catheterization.[6] The phonocardiograms were recorded simultaneously utilizing a logarithmic filter and a cathode-ray photographic recorder at a paper speed of 25 or 75 mm. per second, generally the latter. Fourteen patients without mitral stenosis, who did not have an end-diastolic atrioventricular pressure gradient, and 11 patients with mitral stenosis who had such a gradient were studied.

Figure 1 shows results which are representative of those obtained in all patients without mitral stenosis. The first heart sound began simultaneously with both the onset of left ventricular contraction, as indicated by the beginning of the left ventricular pressure ascent, and with mitral valve closure, as indicated by the peak of the c wave of the left atrial pressure tracing. In contrast, in all patients with mitral stenosis the first vibrations of the first heart sound were not coincident with the onset of left ventricular contraction; they occurred when the left ventricular pressure reached the level of the elevated left atrial pressure, at which time the mitral valve closed and the left atrial c wave was inscribed (fig. 2 and 3). These observations indicate that the opening vibrations of the first heart sound result from closure of the mitral valve, rather than from left ventricular contraction.

However, as has been noted above, in the absence of mitral or tricuspid stenosis, atrioventricular valve closure occurs coincident with the onset of ventricular contraction. Splitting of the first heart sound would then be related to the slight asynchronomy in the onset of ventricular contraction which normally occurs.[7-9] Figure 4 represents the average of the results obtained in 13 individuals without cardiac disease[7] and indicates that the onset of left ventricular contraction precedes the onset of right ventricular contrac-

From the Clinic of Surgery, National Heart Institute, Bethesda 14, Md.

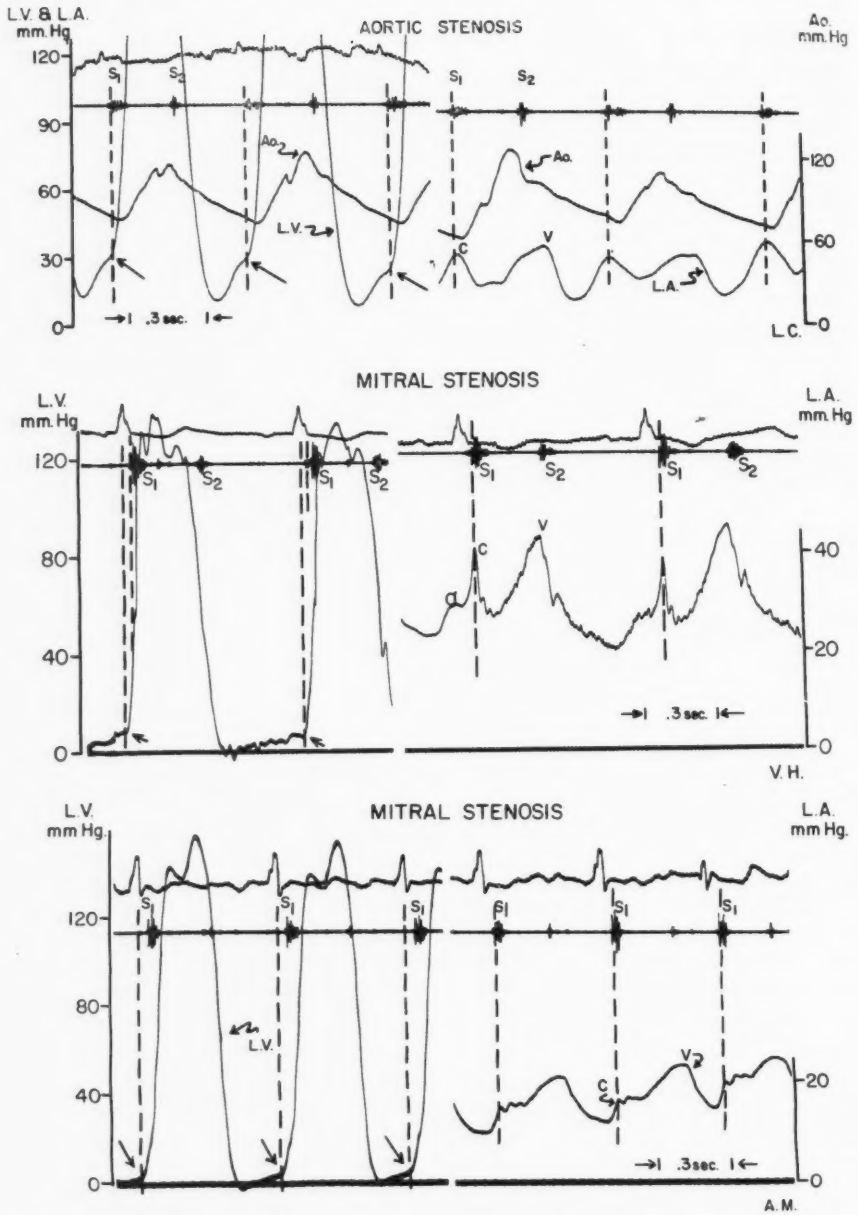


FIG. 1 *Top.* Simultaneous phonocardiogram and left heart pressure pulses in a patient with aortic stenosis but without mitral stenosis. S_1 and S_2 represent the two heart sounds. *L.A.* = left atrium. *L.V.* = left ventricle. *Ao.* = central aorta.

FIG. 2 *Middle.* Simultaneous phonocardiogram and left ventricular (*left*) and left atrial (*right*) pressures. Symbols same as figure 1.

FIG. 3 *Bottom.* Simultaneous phonocardiogram and left ventricular (*left*) and left atrial (*right*) pressures. Symbols same as figure 1.

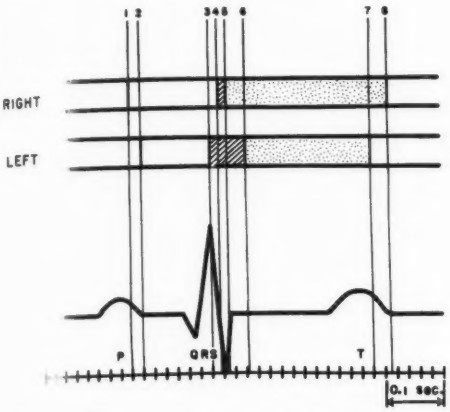


FIG. 1. Diagrammatic representation of the average timing of electrical and mechanical events on both sides of the heart in normal subjects. *(1)* Onset of right atrial contraction, *(2)* onset of left atrial contraction, *(3)* onset of left ventricular contraction, *(4)* onset of right ventricular contraction, *(5)* onset of right ventricular ejection, *(6)* onset of left ventricular ejection, *(7)* termination of right ventricular ejection, *(8)* termination of right ventricular ejection. *Striped areas,* ventricular isometric contraction, *stippled areas,* ventricular ejection. Data obtained with Drs. A. P. Fishman and A. Cournand.[7] *(Reproduced by permission from Circulation Research, 4: 100, 1956.)*

tion by a brief interval. It is also of interest that while the left ventricle begins to contract before the right ventricle, its ejection commences later. On the other hand, left ventricular ejection normally ends before right ventricular ejection (fig. 4) and the normal splitting of the second heart sound therefore consists of the aortic component followed by the pulmonic component.

It has been observed that there is no consistent delay in the onset of left ventricular contraction, but there is prolongation of left ventricular ejection in patients with the electrocardiographic configuration of complete left bundle-branch block.[10] This correlates with the phonocardiographic observation of a single first heart sound,[9, 11] but a paradoxically split second heart sound, with a delayed aortic component, in many of these patients.[11, 12]

The duration of ventricular ejection is also prolonged by an augmentation of stroke volume or a marked increase in the pressure against which the ventricle ejects.[13] These observations afford an explanation for the abnormally widened splitting of the second heart sound in patients with atrial septal defect[14] or pulmonic stenosis[15] in whom the pulmonic component is delayed, and in patients with patent ductus arteriosus or aortic stenosis[12] in whom the aortic component is delayed.

SUMMARY

Evidence for the valvular origin of the first heart sound was obtained by simultaneous phonocardiograms and pressure pulses from the left atrium and left ventricle in patients with mitral stenosis. It was consistently observed that the first heart sound begins at the time of mitral valve closure, significantly after the onset of left ventricular contraction. Hemodynamic observations which explain the splitting of heart sounds in the normal and in diseased states were briefly reviewed.

SUMMARIO IN INTERLINGUA

Le prova del origine valvular del prime sono cardiac esseva obtenite per medio de phonocardiogrammas registrate simultaneemente con determinationes del pulsos de pression ab le atrio sinistre e le ventriculo sinistre in patientes con stenosis mitral. Esseva observate uniformemente que le prime sono cardiac comencia al tempore del clausion del valvula mitral, significativemente plus tarde que le declaration del contraction sinistro-ventricular. Es presentate un breve revista de observationes hemodynamic que expica le fission de sonos cardiac in statos normal e pathologic.

REFERENCES

1. BRAUNWALD, E., MOSCOVITZ, H. L., AMRAM, S. S., LASSER, R. P., SAPIN, S. O., HIMMELSTEIN, A., RAVITCH, M. M., AND GORDON, A. J.: The hemodynamics of the left side of the heart as studied by simultaneous left atrial, left ventricular, and aortic pressures; particular reference to mitral stenosis. Circulation **12**: 69, 1955.
2. —, —, —, —, —, —, —, AND —: Timing of electrical and mechanical events of the left side of the human heart. J. Applied Physiol. **8**: 309, 1955.

3. MESSER, A. L., COUNIHAN, T. B., RAPPAPORT, M. B., AND SPRAGUE, H. B.: The effect of cycle length on the time of occurrence of the first heart sound and the opening snap in mitral stenosis. Circulation. **4**: 576, 1951.
4. WELLS, B.: The assessment of mitral stenosis by phonocardiography. Brit. Heart J. **16**: 261, 1954.
5. KELLY, J. J.: Diagnostic value of phonocardiography in mitral stenosis. Am. J. Med. **19**: 862, 1955.
6. MORROW, A. G., BRAUNWALD, E., HALLER, J. A., JR., AND SHARP, E. H.: Left heart catheterization by the transbronchial route: technic and applications in physiologic and diagnostic investigations. Circulation **16**: 1033, 1957.
7. BRAUNWALD, E., FISHMAN, A. P., AND COURNAND, A.: Time relationship of dynamic events in the cardiac chambers, pulmonary artery and aorta in man. Circulation Research **4**: 100, 1956.
8. LEATHAM, A.: Splitting of the first and second heart sounds. Lancet **2**: 607, 1954.
9. MCKUSICK, V. A., REAGAN, W. P., SANTOS, G. W., AND WEBB, G. N.: The splitting of heart sounds. Am. J. Med. **19**: 849, 1955.
10. BRAUNWALD, E., AND MORROW, A. G.: The sequence of ventricular contraction in human bundle branch block. Am. J. Med. **23**: 205, 1957.
11. MCKUSICK, V. A.: Symposium on cardiovascular sound. Circulation **16**: 414, 1957.
12. GRAY, I. R.: Paradoxical splitting of the second heart sound. Brit. Heart J. **18**: 21, 1956.
13. BRAUNWALD, E., SARNOFF, S. J., AND STAINSBY, W. N.: Determinants of the duration and mean rate of ventricular ejection. Circulation Research **6**: 319, 1958.
14. LEATHAM, A., AND GRAY, I. R.: Auscultatory and phonocardiographic signs of atrial septal defect. Brit. Heart J. **18**: 193, 1956.
15. —, AND WEITZMAN, D.: Auscultatory and phonocardiographic signs of pulmonary stenosis. Brit. Heart J. **19**: 303, 1957.

Studies of the Mechanism of Gallop Sounds

By JAMES J. LEONARD, M.D., ARNOLD M. WEISSLER, M.D., AND JAMES V. WARREN, M.D.

The material of this presentation has been published in Annals of Internal Medicine **48**: 580, 1958, Circulation **17**: 1007, 1958, and **18**: 165, 1958, and British Heart Journal (in press).

PQ Interval, Pressure Difference Across the Mitral Valve and Amplitude of the First Sound in Dogs with Atrioventricular Block

By HELMUT SIECKE AND HIRAM E. ESSEX

The material of this presentation was published in American Journal of Physiology **191**: 469, 1957.

Genesis of Pistol-Shot and Korotkoff Sounds

By Ramon L. Lange, M.D., and Hans H. Hecht, M.D.

The study of spontaneous and induced sounds from the arterial system affords certain obvious advantages over the study of cardiac sounds and murmurs. The simple physical system, relative accessability, multiple sites, and the ease of production of phenomenon in both normal and abnormal states are a few of the advantages.

As is seen in figures 1 and 2, these sounds, when spontaneous, are brief, of low frequency, and rather high intensity. They would seem to be temporally related to the pulse wave.

Figure 1 shows in the first two lines (camera speed as in fig. 2), Korotkoff sounds (at times 2 per pulse because of the dicrotic pulse), and brachial artery pressure below a blood pressure cuff inflated to between systolic and diastolic pressures in the top 2 lines and with no cuff pressure in the lower line (slower camera speed). Note that the relationship of sounds and pressure is the same in both types of sounds (which causes the usually erroneous conclusion that there is "zero diastolic pressure"), suggesting similar mechanism of production.

Figure 2 shows that not only does the sound precede the pressure by 10 to 12 msec., but when the sound is recorded 25 cm. above the site of pressure recording (line II) or 25 cm. below the site of pressure record (line III), it is apparent that the sound has a transmission velocity of a pulse wave (8 to 10 M. per second. Similar results are obtained by the use of a force transducer and microphone system which measures sound and vessel wall movement.

Whatever the genesis of either type of sound, these observations do not support a theory which requires sudden movement of the vessel wall. No pressure phenomenon can be recorded at the source of the sound at the instant the sound is produced.

Figure 3 illustrates in general terms a wave of high energy moving at low velocity along an elastic vessel in physical continuity with a low energy segment. The physical considerations would cause transfer of energy from a high to a low system at a speed greater than pulse wave velocity. This energy transfer, under ordinary circumstances, is absorbed by

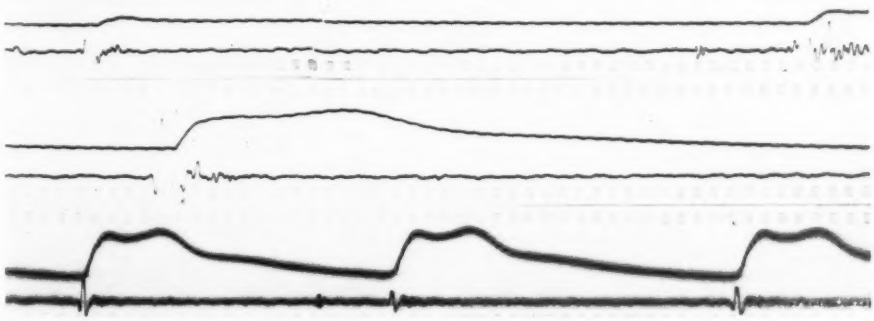


Fig. 1. Simultaneous Korotkoff sounds and pressure taken from a point one cm. below the cuff edge. Line III at slower film speed shows the transition from Korotkoff sounds to spontaneous sounds indicated by the change to a lower frequency. Note that the time relationship remains the same. It is interesting that the extreme "dicrotic" pulse had two peaks with duplication of Korotkoff sounds at cuff pressure near systolic levels. *(Reprinted from Circulation* **13:** *873, 1956.)*

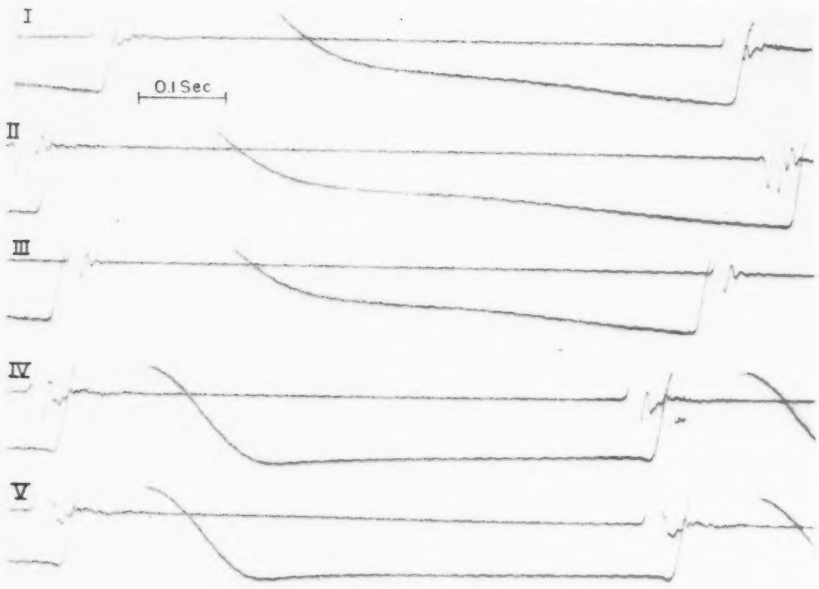
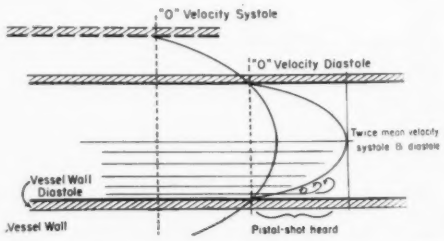


FIG. 2. Simultaneous records of pressure in femoral artery with microphone: I, over needle tip; II, 25 cm. above the needle; III, 25 cm. below the needle; IV and V, 25 cm. above the needle tip (umbilicus), but needle rotated 180° around long axis. *(Reprinted from Circulation* **13:** *873, 1956.)*

the low energy system, and in consequence the transition period should be silent. A critical rate of energy release might cause uneven flow to the extent of audible sound production. These considerations suggest that the presence or absence of sound would be determined by the rate of energy change of the system. The factors influencing this are expressed in the general equation of figure 3.

To test this concept, changes in appropriate parameters of energy were induced in order to seek a correlation with the occurrence of sounds. Table 1 shows this relationship in normal individuals in response to drugs or stress.

Figure 4 allows the influence of anacrotic slope (*dP/dt* of fig. 3) of the pulse curve to be separated from the other variables in a young man with aortic insufficiency who, over a 20 month period, lost his previously prominent pistol shot sounds in all but the femoral



The Factors Contributing to the Rate of Kinetic Energy Changes During Early Systole:

$$dE = k \; f(\Delta P, \; dP/dt, \; dA/dt, \; v)$$

Where ΔP is pulse pressure, A is cross-sectional area, and v is mean linear velocity.

FIG. 3. A schematic representation of the change in velocity profile of laminar flow patterns which occurs with increasing caliber without change in mean linear velocity. *(Reprinted from Circulation* **13:** *873, 1956.)*

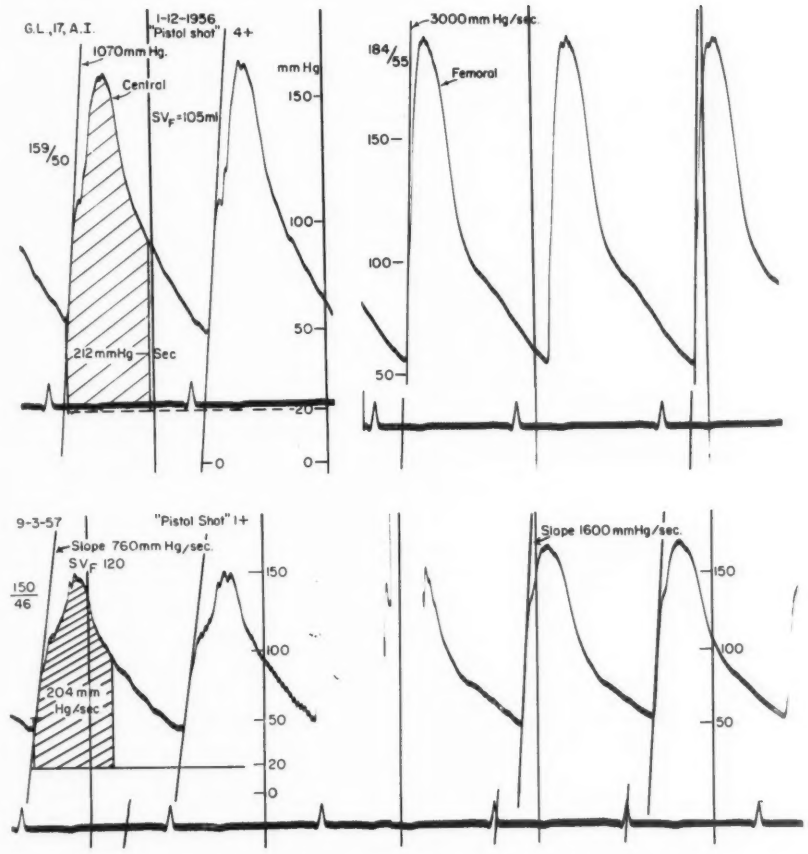


FIG. 4. Studies on an individual with aortic insufficiency over a period during which the intensity of spontaneous sounds diminished strikingly. The only change in parameters was the decrease in anacrotic pressure slope. Flow, pulse pressure and elasticity remained essentially unchanged.

TABLE 1.—*Relations of Flow, Rate, Duration and Degree of Pressure Rise, Blood Pressure, and Vascular Sounds (Reprinted from Circulation* **13**: *873, 1956)*

Subject		Cardiac output (L./min.)	Stroke volume (ml./beat)	Arterial pressure (mm. Hg)		Vascular sounds	Anacrotic slope of arterial pulse (mm./Hg/sec.)		$\Delta P/t$	Remarks
				Cuff	Direct		Central	Peripheral		
J. M.	Normal	7.2	120	130/70	130/70	—		960	60/0.07	
		9.0	121	125/65	125/65	++*		1200	60/0.05	10% O_2 inhalation
		18.7	170		130/70	++++		1400	60/0.04	10% O_2, 50 mg. Priscoline, i.v.
W. .	Normal	7.7	101		140/80	—		1000	60/0.06	10% O_2 inhalation
		9.4	94		150/60	+*		1200	90/0.08	10% O_2 inhalation, 50 mg. Priscoline, i.v.
		14.7	136		175/75	+++		1500	100/0.07	

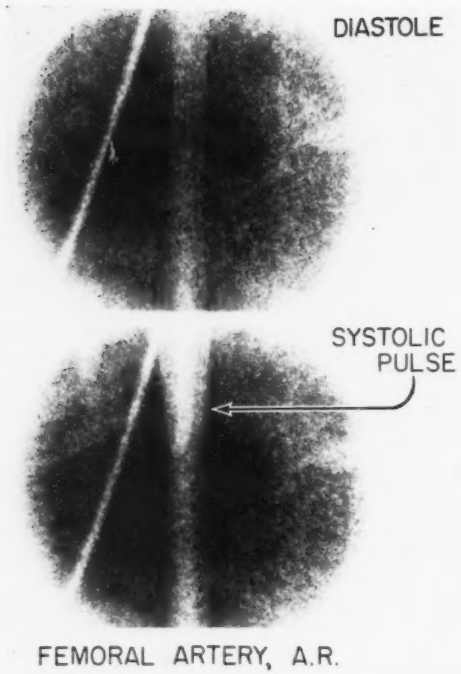


FIG. 5. The degree of femoral artery expansion with systolic pulse is indicated by this cinefluorex study with proximal injection of Hypaque.

artery, but in whom the only essential parameter change was an almost 50 per cent fall in anacrotic pulse pressure rise. This was presumably due to a change in myocardial contractility occurring in the interval between studies.

The influence of wall elasticity is paramount since the parameters other than dA/dt may be high in an inelastic system without the production of sound. Figure 5 shows the marked degree of femoral artery systolic expansion in an individual exhibiting spontaneous sounds as demonstrated by proximal arterial injection of Hypaque and "cinefluorex" study. Two sequential film frames are shown.

In conclusion, the temporal relations between sounds and pressures in the vascular system require an explanation which deals with rapid energy changes in the time immediately preceding systole. The general formulation of the theory can be supported by alteration in the energy components and, to a certain extent, the effects of separate components can be assessed. An additional conclusion is worthy of mention, that is that in this particular case, sounds of a character not dissimilar to heart sounds are produced without setting into vibration any physical structure but arising rather from disturbed flow alone. These spontaneous sounds may be of considerable clinical importance; when present they indicate nigh rates of pulsatile flow from vigorous ventricular ejection into a system of normal elasticity.

Correlation of Heart Sounds and Murmurs with Pressure During Left Heart Catheterization

By Alvin J. Gordon, M.D., Leonard Steinfeld, M.D., Maurice Dunst, M.D., and Paul A. Kirschner, M.D.

The development of a method[1, 2] to obtain multiple equisensitive pressure pulses in the left atrium, left ventricle and aorta in the heart exposed at operation, and to display them together, with the same baseline, made it possible to visualize the mechanical events of the cardiac cycle and to measure their phase with great accuracy. It was apparent that the method lent itself naturally to a study of the genesis of heart sounds and murmurs, provided it were possible to record the sounds simultaneously and with sufficient fidelity.

Methods

An oscilloscopic recorder was designed* utilizing a single-gun electron tube, in which the beam is split into 8 parts by an electron switch operating at the rate of 26,000 per second. This unit contains an electrocardiography channel, two phonocardiography channels, three pressure channels and finally two "pressure difference channels" by means of which continuous pressure differences between 2 adjacent channels may be obtained by electronic subtraction of the outputs of the 2 pressure transducers involved.

With this recorder, it is possible to obtain 8 parameters simultaneously without significant parallax error. The only timing error lies in the transmission delay of the pressure events through the plastic tubing-stopcock-pressure transducer system, which we have found on a previous occasion[3] and have recently verified to be no greater than 0.005 or 0.006 seconds. When our records are taken at a paper speed of 50 mm. per second this delay may be ignored but at the fast speed of 150 mm. per second it must be taken into account.

Triple equisensitive pressure pulses have been obtained in the human heart during left heart catheterization by the transbronchial route.[4] Whenever possible fine polyethylene catheters have been left in place in the left atrium and left ventricle, and the bronchoscope removed. Central aortic pulses have been obtained simultaneously by catheterization with a fine vinyl plastic catheter through the right brachial artery. Placement of the latter close to the aortic valve has often proven difficult, however, the fidelity of the system may easily be verified, as any error in placement of the catheter tip becomes apparent in the tracing as a slight phase difference in the pressure pulses. Damping and other artifacts are similarly exposed.

Whenever possible right heart catheterization has been performed simultaneously and phonocardiograms recorded together with pressure events on the right side of the heart as well. Heart sound records from the chest wall have been obtained by means of the Sanborn dynamic or the Peiker crystal microphones, with the aid of pass-band filters. Conditions during the left heart catheterizations have not been ideal from the standpoint of heart sound recording. This accounts for some of the deficiencies apparent in our phonocardiograms.

Our series, which amounts to 50 cases at this time (February 1957), consists of adult patients with acquired mitral or aortic valve lesions who are candidates for cardiac surgery.

Results

Results, which are here reported in preliminary form, may perhaps be best illustrated by reference to a group of representative tracings.

Figures 1 and 2 were taken several seconds apart from the same patient, the first at a paper speed of 50 mm. per second and the second at 150 mm. per second. In figure 1 note that the second beat is a ventricular premature contraction. Although it is not possible to localize the ectopic focus from lead II of the electrocardiogram, the time interval from Q2 to left ventricular systole is about the same in the premature beat as in the nor-

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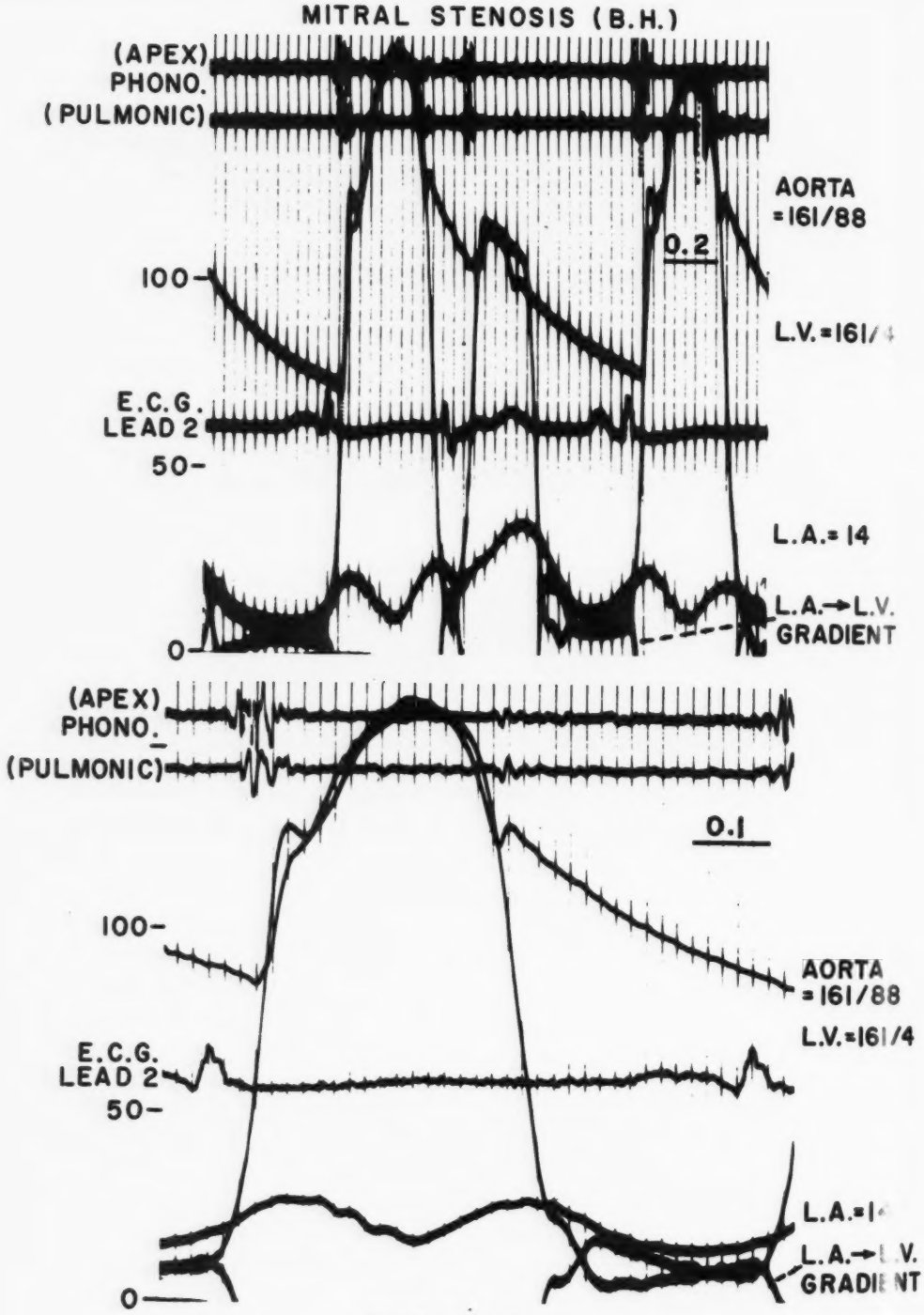
This investigation was supported in part by a research grant (H-2168) from the National Heart Institute, U.S. Public Health Service.

*Made by Electronics for Medicine, White Plains, N. Y.



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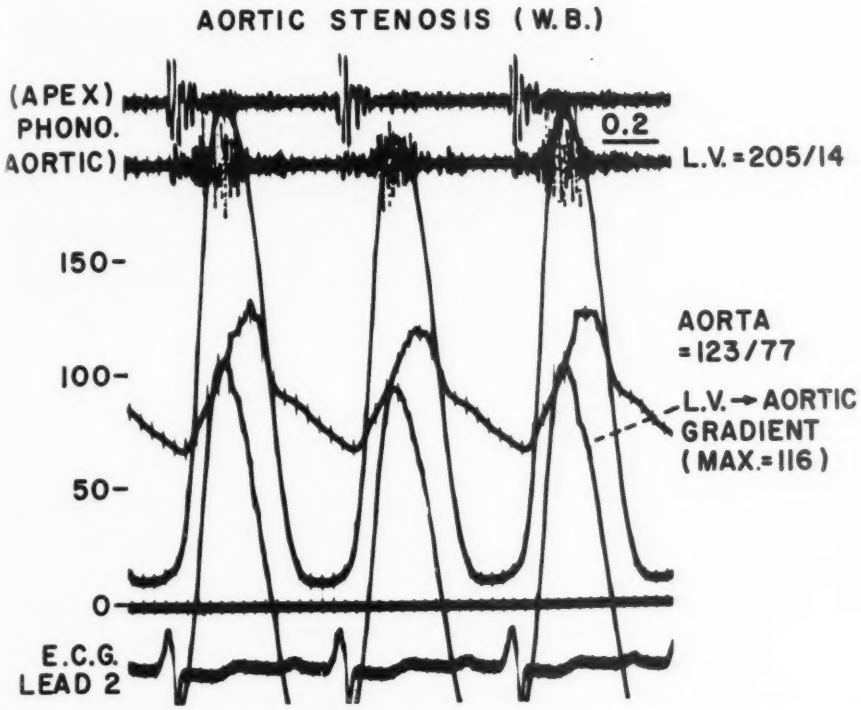

FIG. 3. Aortic stenosis, recorded during left heart catheterization. Paper speed equals 50 mm. per second; time lines 0.04 seconds.

mally conducted beats, suggesting that the ectopic focus is in the left ventricle. The premature contraction is barely sufficient to open the aortic valve.

Note that the first heart sound is of shorter duration and lesser intensity in the premature beat, which may be explained by the small quantity of blood ejected.

In the first beat, the second heart sound coincides exactly with the dicrotic notch of the aortic pressure pulse and the closure of the aortic valve. This is also true of the premature beat. (The phase of reduced ejection of the left ventricle in the premature beat is slightly distorted.) A sound of high intensity which occurs at the pulmonic area shortly after the peak of ventricular systole in the third beat, does not coincide with any of the pressure events on the left side of the heart. That this is an artifact is attested to by its absence in the remainder of the record.

In figure 2 taken at fast speed, the correlation of the heart sounds with the events of the cycle on the left side of the heart is more readily apparent. This photograph also demonstrates, with greater clarity, the continuous pressure difference across the stenotic mitral valve (here labeled "L.A. to L.V. gradient"). It is basically M-shaped. Although the low pitched diastolic murmur of mitral stenosis is

FIG. 1 *Top.* Electric, mechanical and acoustic events in a patient with mitral stenosis, recorded during left heart catheterization. Paper speed equals 50 mm. per second; time lines 0.04 seconds.

FIG. 2 *Bottom.* The same patient as in figure 1, recorded a few seconds later. Paper speed equals 150 mm. per second; time lines 0.02 seconds.

not well depicted in this illustration, it is apparent (and it is also a well-known clinical observation) that the murmur is loudest in early and late diastole. This corresponds to the periods of maximum pressure difference and presumably maximum blood flow across the valve.

Figure 3, from a patient with aortic stenosis, shows several characteristic features. The ventricular pressure pulse has a peaked contour (similar to that found in the right ventricle in pulmonic valvular stenosis). The aortic pressure pulse has a slow upstroke, delayed peak and poorly defined dicrotic notch. The continuous pressure difference across the aortic valve ("ejection gradient") is shaped like an inverted V. In most beats in this case the maximum pressure difference precedes the peak of ventricular pressure.

The aortic systolic murmur begins a short time after the first sound; the latent period representing part of the time interval between the beginning of ventricular systole and the beginning of ejection (isometric contraction phase). The murmur demonstrates the characteristic diamond shape, which in each heart beat may be seen to correlate closely both in time and intensity with the continuous pressure difference across the valve. From beat to beat, the intensity of the murmur also varies directly with the height of the pressure difference.

The second sound, visible on the aortic phonocardiogram, apparently arises from the pulmonic valve, as it occurs much later than the closure of the aortic valve as determined by the cross-over point of ventricular and aortic pressures during diastole.

REFERENCES

1. Gordon, A. J., Braunwald, E., and Ravitch, M. M.: Simultaneous pressure pulse in the human left atrium, ventricle and aorta: Preliminary communication. Circulation Research **2**: 432, 1954.
2. Braunwald, E., Moscovitz, H. L., Amram, S. S., Lasser, R. P., Sapin, S. O., Himelstein, A., Ravitch, M. M., and Gordon, A. J.: The hemodynamics of the left side of the heart as studied by simultaneous left atrial, left ventricular, and aortic pressures. Particular reference to mitral stenosis. Circulation **12**: 69, 1955.
3. Gordon, A. J., Braunwald, E., Moscovitz, H. L., and Amram, S. S.: Delay in transmission of a pressure impulse through a cardiac catheter and vinyl plastic tubing. J. Appl. Physiol. **8**: 573, 1956.
4. Morrow, A. G., Braunwald, E., Haller, J. A., Jr., and Sharp, E.: Left heart catheterization by the transbronchial route: Technic and applications in physiologic and diagnostic investigations. Circulation **16**: 1033, 1957.

Intracardiac Phonocardiography

Correlation of Mechanical, Acoustic and Electric Events of the Cardiac Cycle

By Howard L. Moscovitz, Ephraim Donoso, Ira J. Gelb, and Walter Welkowitz

ATTEMPTS to record heart sounds and murmurs at their site of origin are not new. For obvious reasons, sounds picked up from the surface of the thorax are not a true representation of the actual vibrations of the cardiac valves and walls. Thus, physiologists have attempted to move their recording instrument closer to the sound source by placing microphones in the esophagus,[1, 2] by suturing microphones to the myocardium in experimental animals,[3] by applying suction microphones directly to the surface of the human heart,[4] and finally by introducing the microphone into the interior of the cardiac chambers themselves. Intracardiac microphones have been described by Yamakawa,[5] Soulié,[6] Lewis,[7] and by Luisada.[8] We have used a ceramic microphone sealed in the tip of a standard double-lumen cardiac catheter to correlate the mechanical and acoustic events of the cardiac cycle in animals with experimental valvular lesions and arrhythmias and in patients with heart disease.

Methods and Materials

The microphone consists of a modified barium titanate element called Glennite,* which is endowed with piezoelectric properties by special polarizing treatment. The ceramic element of the microphone 1.2 mm. in diameter and 15 mm. in length, is fixed at one end of the catheter shell to form a cantilever (fig. 1). As the sensitive diaphragm vibrates in accordance with the sound, a rigid pointer transmits the mechanical motion to the ceramic. Because of its piezoelectric property, the ceramic on bending generates a voltage which is transmitted along the electric leads to the external circuit amplifiers and oscillographic recorder. The response is flat between 20 and 3,000 c.p.s.

Results

Normal Heart Sounds. With the microphone located in the dog's left atrium, 4 distinct sounds can be detected (fig. 2). More precise identification of heart sounds can be achieved by recording them simultaneously with multiple pressure pulses.

In an open-chest dog, it is possible to record synchronously pressure tracings from the left atrium, ventricle and aorta, together with an intracardiac phonocardiogram and an electrocardiogram (fig. 3). Since an intracardiac microphone records sounds from one side of the heart with minimal interference from valve areas on the opposite side, analysis of the individual heart sounds is considerably simpler. The first component of the first sound appears to be synchronous with atrioventricular pressure curve crossing (apparently the time of mitral valve closure); the second component of the first sound occurs at

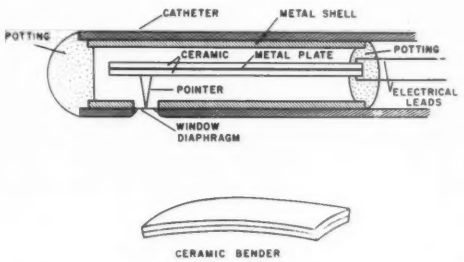

FIG. 1. Cross-sectional diagram of intracardiac microphone. The ceramic element is 1.2 mm. in diameter and 15 mm. in length.

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Aided by a grant from the New York Heart Association.

*Manufactured by Gulton Industries, Metuchen, N. J.

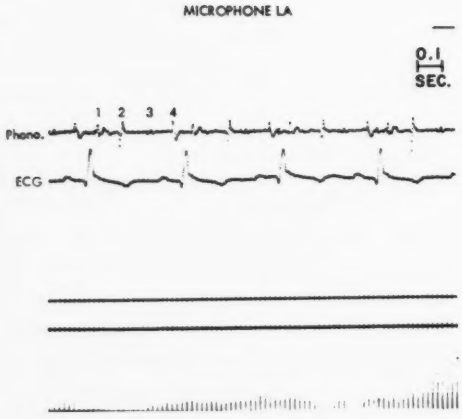

FIG. 2. Left atrial heart sounds in a dog. Note that the first heart sound has 2 distinct components.

the time of aortic valve opening. The second heart sound appears at or immediately before the incisura. The third sound, when recorded, occurs on the downstroke of the V wave. From such a tracing one can see that the interval between the 2 components of the first sound equals isometric contraction. The interval between the second component of the first heart sound and the second heart sound is total ejection. Total systole is bounded by

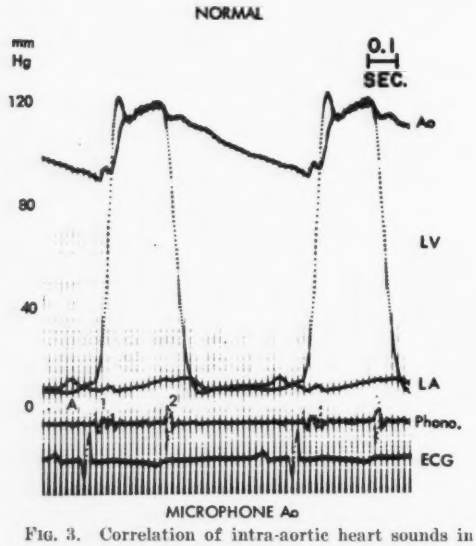

FIG. 3. Correlation of intra-aortic heart sounds in a dog with mechanical events of the cardiac cycle of the left heart.

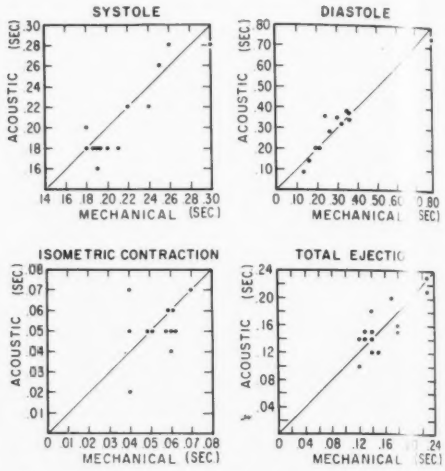

FIG. 4. Relationship between mechanical and acoustic events of the cardiac cycle.

the first component of the first heart sound and the second sound. Total diastole is equal to the time elapsed between the second sound and the initial vibrations of the first heart sound.

It is conceivable then that one could determine the duration of the phases of the cardiac cycle with a good deal of precision, from a well written phonocardiogram. In figure 4, the length of the individual phases as measured from the pressure curves is plotted on the horizontal axis, and their duration determined from the intracardiac phonocardiogram on the vertical axis. Good correlation exists for total diastole, systole and ejection, only fair correlation for isometric contraction. If, however, one would be satisfied to obtain the duration of isometric contraction from the phonocardiogram with a permissible error of $\pm$ 0.02 second, the correlation would be quite good, all points but 1 falling within this area.

Premature Ventricular Contractions. After a frustrate premature contraction, blood is ejected from the ventricle during the next beat with an increase in volume and velocity of flow. This is often sufficiently great to exceed the critical Reynold's number, result in turbulent flow, and give rise to a murmur detectable when the microphone is in one of the

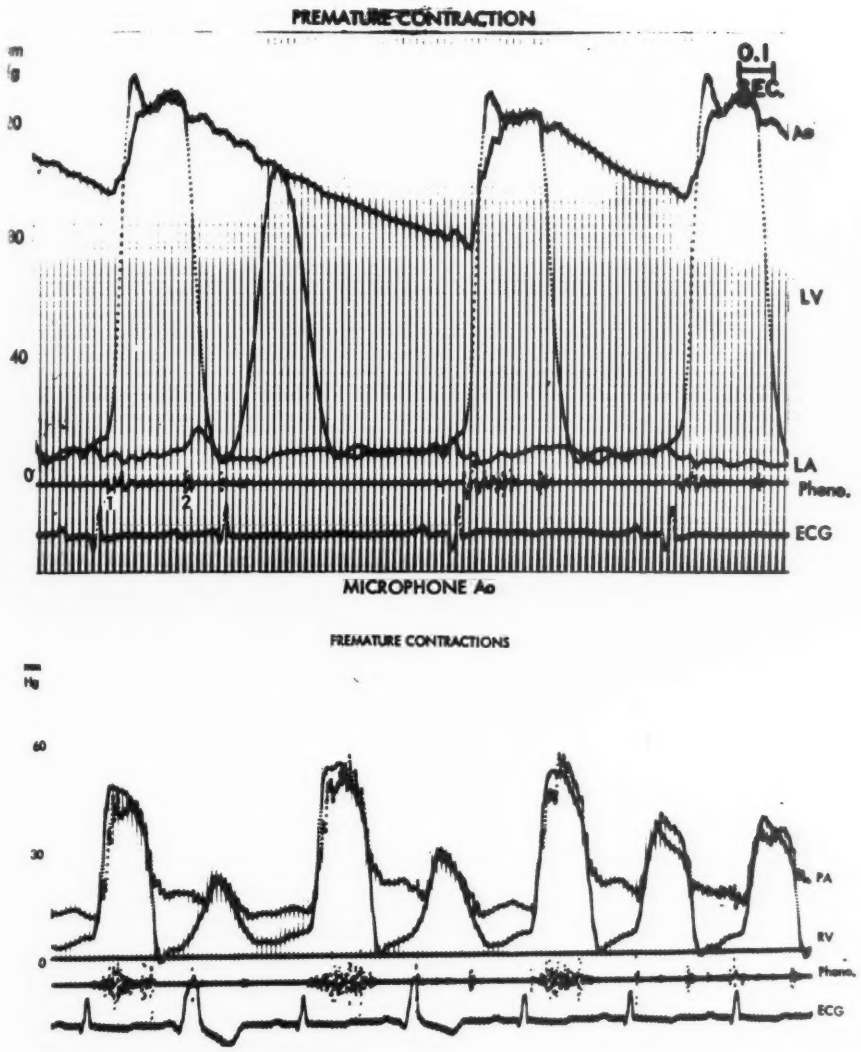

FIG. 5. *Top.* Premature ventricular contraction. Note that the microphone in the aorta detects a systolic flow murmur during the first normal beat following a frustrate premature contraction. *Bottom.* Bigeminal rhythm. The normal sinus beats are accompanied by systolic flow murmurs, since the ventricle has been incompletely emptied during the previous beat.

great vessels (fig. 5 *Top*). This can also be seen on the right side of the heart during a short run of bigeminal rhythm (fig. 5 *Bottom*). Flow murmurs are detectable in the pulmonary artery when blood is ejected from the fuller-filled ventricle during the regular sinus beats.

Aortic and Pulmonic Stenosis. A constricting suture about the aortic root in a dog gives rise to aortic stenosis. The diamond-shaped murmur of aortic stenosis is generated at the stenotic area and does not depend upon transmission through the chest wall for its characteristic configuration (fig. 6 *Top*). The maxi-

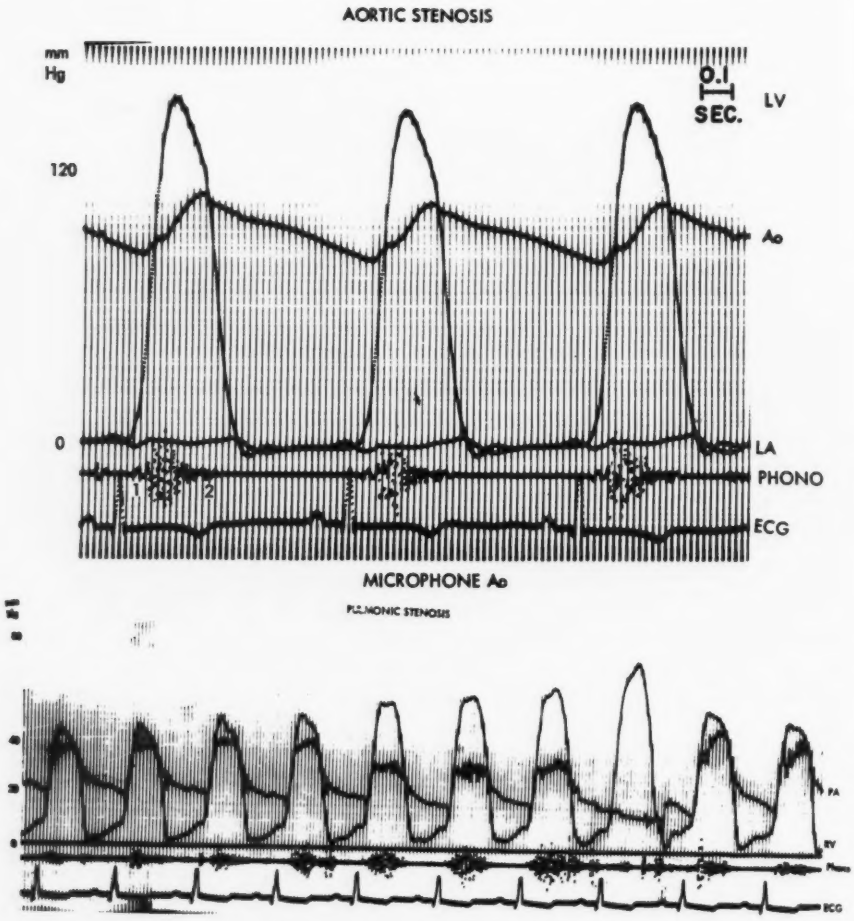

FIG. 6. *Top.* Aortic stenosis in a dog. The diamond-shaped murmur begins after the onset of aortic ejection and reaches its maximum intensity significantly later than the anacrotic notch. *Bottom.* Pulmonic stenosis in a dog. Note that the intensity of the systolic murmur depends on flow as well as orifice area.

mum intensity of the murmur occurs after the anacrotic notch suggesting that the greatest flow occurs after this point. In simulated pulmonic stenosis, a diamond-shaped murmur is produced whose intensity is modified by the interrelationship of orifice area, magnitude of flow and velocity of discharge. It can be seen that the murmur is louder with moderate stenosis than during such severe degrees of stenosis that flow through the valve is markedly restricted (fig. 6 *Bottom*).

Mitral Stenosis. The presystolic rumble of mitral stenosis at times is difficult to record with some types of phonocardiographic equipment. In figure 7 experimental mitral stenosis is produced by a constricting suture encircling the mitral annulus. Note the atrial sound in the first beat before the suture about the mitral annulus is tightened and the loud presystolic murmur which develops as the left atrial pressure rises.

Aortic Insufficiency and Stenosis. Of considerable interest was the fact that the murmur of aortic insufficiency shown in the first

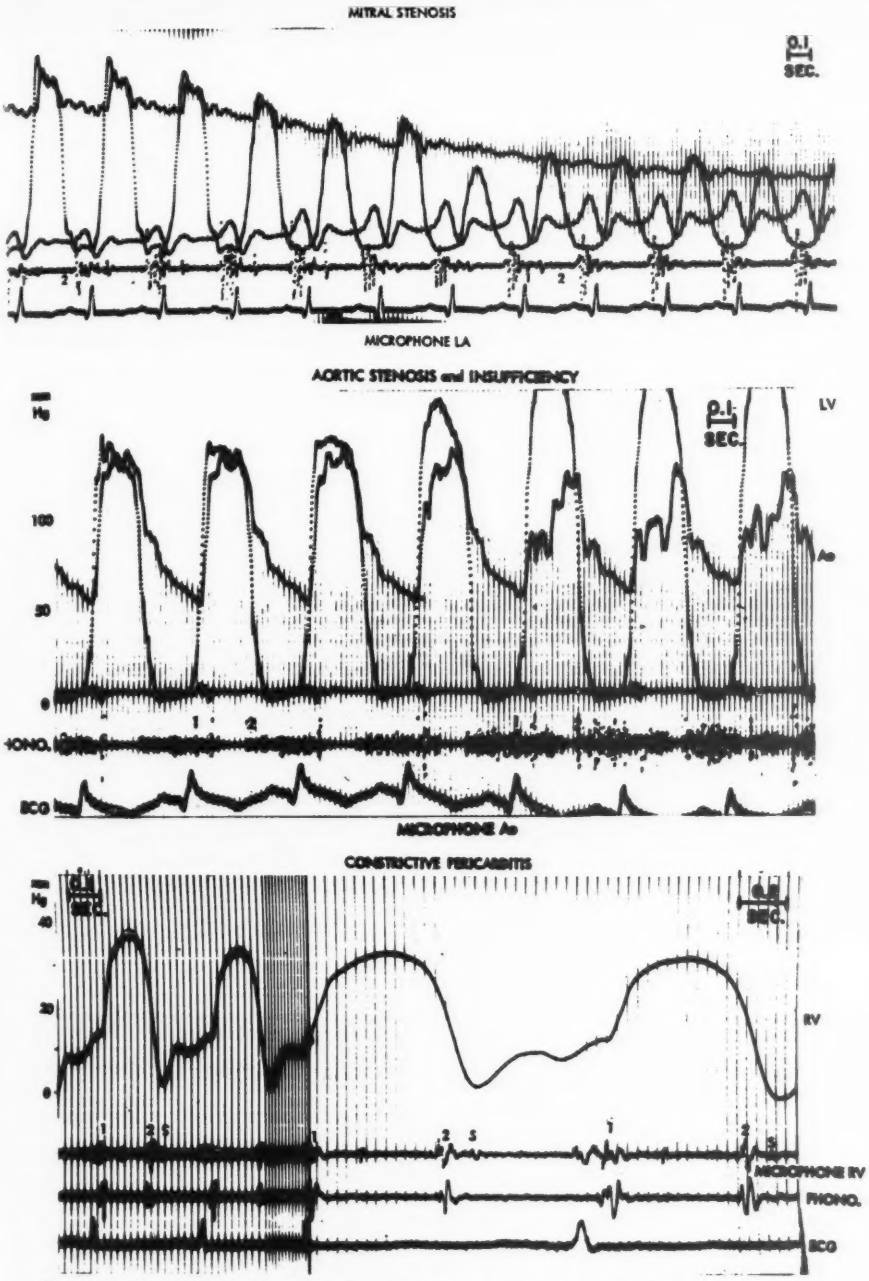

FIG. 7 *Top.* Mitral stenosis in a dog. The presystolic murmur is detected by the microphone located in the left atrium and increases in intensity as the left atrioventricular pressure gradient rises.

FIG. 8 *Middle.* Superimposition of aortic stenosis on a dog with aortic insufficiency. The microphone in the aorta initially records a long diastolic murmur during uncomplicated aortic regurgitation. As stenosis is superimposed, not only does a systolic murmur appear, but the diastolic murmur becomes more intense.

FIG. 9 *Bottom.* Right ventricular sounds in a patient with constrictive pericarditis. The early diastolic sound(s) is more easily identified inside the ventricle than by the conventional chest wall phonocardiogram (*phono.*).

2 beats of figure 8 becomes louder with the superimposition of aortic stenosis. This apparently was due to an increase in turbulence as a well maintained regurgitant flow traversed the narrowed aortic orifice.

Constrictive Pericarditis in Man. The early diastolic sound of constrictive pericarditis which is an extremely valuable diagnostic sign occurs at the lowest point on the ventricular curve (fig. 9). It apparently occurs at the time the rapidly filling ventricle abruptly meets the restrictive pericardial envelope and can fill no further without the cost of a marked rise in diastolic pressure.

The versatility of this instrument recommends it for further investigative work in basic hemodynamic problems and as an aid in clinical diagnosis. We visualize that some day, not far off, the cardiac physiologist will be armed with a multipurpose cardiac catheter. This single instrument will not only be capable of obtaining pressures and blood samples for oxygen analysis. It will also permit injection of radiopaque dye directly into any of the cardiac chambers for the more precise delineation of the interior anatomy of the heart. Finally, it will be capable of more accurately localizing cardiac defects by detecting murmurs at their source.

REFERENCES

1. Benjamins, E. E.: L'auscultation et L'enrégistrement des bruits du coeur par voie oesophagienne. J. Physiol. Path. Gén. **16**: 597, 1914.
2. Magri, G., Caruzzo, C., Gamna, G. and Oddone, I.: Oesophageal phonocardiography. Cardiologia **31**: 407, 1957.
3. Wiggers, C. J., and Dean, A. L.: The nature and time relationships of the fundamental heart sounds. Am. J. Physiol. **42**: 476, 1917.
4. Bertrand, C. A., Milne, I. G., and Hollick, R.: A study of heart sounds and murmurs by direct heart recordings. Circulation **13**: 49, 1956.
5. Yamakawa, K., Shionoya, Y., Kitamura, K., Nagai, T., Yamamoto, T., and Ohta, S.: Intracardiac phonocardiography. Am. Heart J. **47**: 424, 1954.
6. Soulié, P., Laurens, P., Bouchard, F., Cornu, C., and Brial, E.: Enregistrement des Pressions et des Bruits Intracardiaques à l'aide d'un Micromanomètre. Bull. et Mém. Sóc. med. hôp. Paris **22**: 713, 1957.
7. Lewis, D. H., Dietz, G. W., Ertugrul, A., Wallace, J. D., and Brown, J. R., Jr.: Intracardiac phonocardiography in man. Clinical Research Proceedings **5**: 166, 1957.
8. Luisada, A. A., and Liu, C. K.: Simple methods for reading intracardiac electrocardiograms and phonocardiograms during left and right heart catheterization. Am. Heart J. **54**: 531, 1957.

Intracardiac Phonocardiography in Mitral and Aortic Value Lesions

By A. A. Luisada, M.D., and C. K. Liu, M.D.

INTRACARDIAC phonocardiography (i.e. phono.) is a recently described technic. Right heart i.c. phono was independently described by Soulié,[1] Lewis et al.[2] and Moscovitz et al. Left heart i.c. phono was described by Luisada and Liu[4–6] who use an entirely different principle which can be applied to either side of the heart.

Methods

Intracardiac phonocardiograms were recorded, according to previous descriptions, by connecting the strain gage channel, by means of a short cable, to the phono channel. The medium and high frequency vibration of the gage were differentiated, amplified, and filtered, then recorded by the phono channel. This system allows one to register the vibrations of the blood within the various chambers without introducing any additional device into the heart.

The intracardiac phonocardiogram was recorded in the bands 60-110, 60-250, or 60-500. Occasionally, the band 30-110 was also used.

Results

Subjects with Normal Valves. Two patients presenting no murmurs were submitted to both right and left catheterization. The pressure tracings revealed no valvular lesions.

Severe Mitral Stenosis. Tracings recorded in the left atrium revealed no systolic murmur in 2 and a few, low frequency, systolic vibrations in decrescendo in 1 case. A third case had an opening snap of the mitral valve. Tracings recorded in the left ventricle of one case (fig. 1) revealed an opening snap of the mitral valve, the largest vibration of which followed the aortic component of the second sound by 0.05 second. Following this snap, a diastolic rumble with presystolic accentuation was clearly visible.

Mitral Stenosis and Insufficiency. The left ventricular tracings revealed abnormalities which were similar to those described for pure stenosis.

The left atrial tracings revealed an opening snap of the mitral valve in 4 cases out of 7. They also revealed the vibrations of a systolic murmur in 5 out of 7 cases.

Mitral Insufficiency. Left ventricle: In two cases, a systolic murmur was recorded. In one, a short and small diastolic rumble was recorded. Left atrium: The left atrium of 3 cases (as well as that of 5 cases with mitral insufficiency and stenosis) revealed the vibrations of a systolic murmur. This was usually shorter and of smaller amplitude after a short diastole. It was better recorded through the catheter than through the needle and became particularly large when the tip of the catheter approached the mitral valve (fig. 2).

Aortic Stenosis and Insufficiency. The trac-

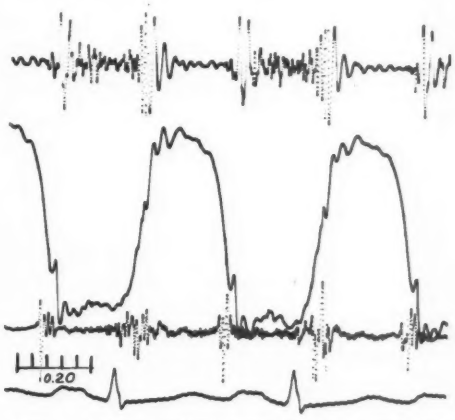

Fig. 1. Case of mitral stenosis. Left ventricular tracings. From above: i.c., phono, pressure, external phono, ECG. Diastolic-presystolic murmur.

From the Division of Cardiology of the Chicago Medical School at Mount Sinai Hospital, Chicago, Ill.

This study was made under the tenure of a Teaching Grant of the National Heart Institute, U.S. Public Health Service, and with the help of Research Grant of the National Heart Institute (H-3416) and the Chicago Heart Association.

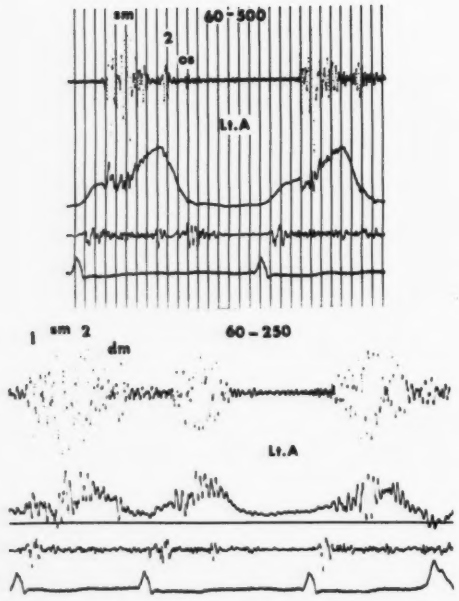

FIG. 2. Left atrial tracings in pure mitral insufficiency. *Upper tracing*, catheter in center of chamber. *Lower tracing*, catheter near the valve. At a distance from the valve, there is a late systolic wave and a short, early systolic murmur. Near the valve, the pressure tracing reveals the thrill and the sound tracing shows a longer systolic murmur.

ings recorded in the ascending aorta chiefly revealed the systolic murmur (fig. 3). A diastolic murmur was apparent in cases with severe insufficiency while it was nonexistent in the others.

At the present stage of our study, we consider that the importance of the various methods in left heart catheterization is as follows: (a) pressure gradients (stenosis), (b) pressure patterns (insufficiency), and (c) sound vibrations (stenosis or insufficiency).

The third method is still being investigated and a complete evaluation will be possible only on the basis of a large number of cases.

ADDENDUM

Since presentation of this paper, the number of cases studied by i.e. phonocardiography of the left heart has reached the number of 45. The interest of the method becomes more and more apparent through a more extensive study.

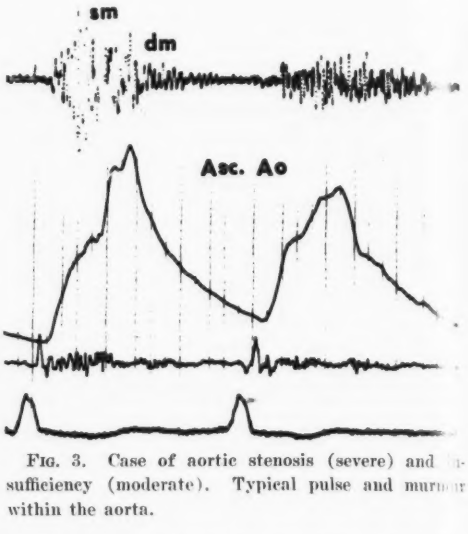

FIG. 3. Case of aortic stenosis (severe) and insufficiency (moderate). Typical pulse and murmur within the aorta.

REFERENCES

1. SOULIÉ, P., BOUCHARD, F., AND CORNU, C.: Le micromanomètre intracardiaque Allard-Laurens. II World Congress of Cardiol., 1954 (also Bull. et mem. Soc. hôp. Paris, 713, 1957).
2. WALLACE, J. O., BROWN, J. R., LEWIS, D. H., AND DEITZ, G. W.: Acoustic mapping within the heart. J. Acoust. Soc. Amer. 29: 9, 1957.
3. MOSCOVITZ, H. L., DONOSO, E., AND GELB, I. J.: The demonstration of flow murmurs by intracardiac phonocardiography. Clin. Res. Proc., April, 1957.
4. LUISADA, A. A., AND LIU, C. K.: Simple methods for recording intracardiac electrocardiograms and phonocardiograms during left or right heart catheterization. Am. Heart J. 54: 531, 1957.
5. LUISADA, A. A., LIU, C. K., ARAVANIS, C., AND TESTELLI, M. R.: Intracardiac vibrations of sonic frequency within the right and left hearts. Acta cardiol. 13: 338, 1958.
6. LIU, C. K., ARAVANIS, C., TESTELLI, M. R., AND LUISADA, A. A.: Intracardiac phonocardiography in mitral and aortic valve lesions. Am. J. Cardiol. 1: 379, 1958.

Present Status of Intracardiac Phonocardiography

By David H. Lewis, M.D., George W. Deitz, M.D., John D. Wallace, A.B. and James R. Brown, Jr., B.S.E.E.

The most important aspect of our studies has been the observation that this technic, using the underwater, barium titanate microphone, provides an exact localization of the production of heart sounds and murmurs.

Figure 1 illustrates the normal intracardiac phonocardiogram from the various chambers of the heart and from the great vessels. Several points may be made:

1. Comparison of similar locations reveals that the sounds from the left side are of greater intensity than those from the right.
2. The first sound is heard throughout and is of greatest intensity in the ventricle.
3. In the ventricle the first major component of the first heart sound is loudest, while in the pulmonary artery and aorta the later components are of greatest intensity.
4. The second sound is heard throughout and is of greatest intensity in the pulmonary artery and aorta.
5. In the aorta and pulmonary artery the second sound represents closure of the respective semilunar valve.
6. The third sound has been observed infrequently and is of greatest intensity in the ventricle; in the right ventricle it is more pronounced in the inflow tract and while this would appear to be the case also for the left ventricle, further studies are needed to be certain about this point.
7. The fourth sound is of greatest intensity in the atrium but may also be heard in the ventricle; it has not been seen in the presence of atrial fibrillation.
8. A systolic murmur is routinely observed in the pulmonary artery but not in the aorta.

In disease states the ability of this technic to localize very precisely the origin of abnormal sounds and murmurs has made it a very valuable diagnostic tool. For example, in left-to-right shunts the sharp localization of the characteristic murmur provides information as to the exact site of the defect, and will do this even when the oxygen studies are equivocal. Conversely, it is also of value in ruling out the presence of suspected intracardiac shunts. In valvular disease, stenosis and/or insufficiency, this technic provides exact information as to the valve or valves involved and will do this even when the hemodynamic data are equivocal.

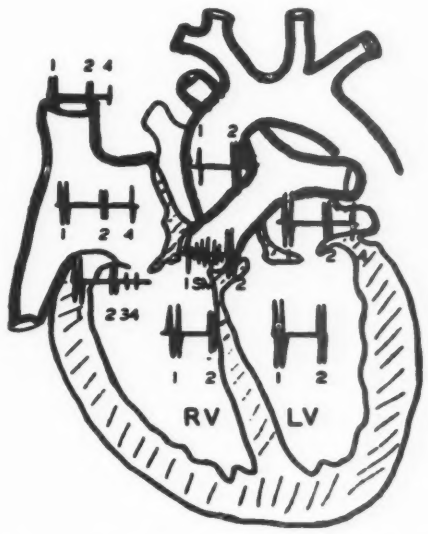

Fig. 1. This illustrates the location and the relative intensity of the sounds in the various heart chambers.

In summary, the status of our studies at present indicates that intracardiac phonocardiography is an extremely valuable diagnostic tool in addition to its potentialities in a further understanding of the genesis of heart sounds.

The Pulmonary Valve in Direct Phonocardiography

By William M. Rogers, Ph.D., Erwin Simandl, M.D., Shivaji B. Bhonslay, M.D., and Ralph A. Deterling, Jr., M.D.

THE pulmonary second sound plays an important role in the clinical diagnosis of congenital and acquired heart diseases. Since phonocardiographic recordings from the chest wall present the pulmonary valve sound as part of a composite of sounds produced by 2 valves of the heart, it was our interest to demonstrate the pulmonary sound by direct phonocardiography.

Cardiac sounds and murmurs heard and recorded at the chest wall under normal and pathologic conditions are composed of audible vibrations associated with different mechanical events of the cardiac cycle occurring at the same time or in close sequence. Therefore, separation and identification of vibrations due to a single event, such as closure of 1 valve, is frequently difficult. The problems increase with anatomic variations, as they occur in congenital malformations of the heart and great vessels and with a combination of such defects. It is reasonable to assume, that recording directly from the surface of the heart, as close as possible to the presumed origin of the single sound will increase the understanding of those vibrations as well as their variation with pathologic conditions.

Direct phonocardiography has been used in the past under experimental conditions. Most investigators have recorded vibrations only from the ventricles. To our knowledge, Wiggers and Dean,[1] were the first to have recorded sounds from the aorta and pulmonary artery as well. Bertrand and associates[2] recently reported an experimental study in dogs employing a stethoscopic bell pick up held in place by suction. They recorded heart sounds and experimentally produced murmurs from all 4 chambers of the heart and from the aorta and pulmonary artery. Impressed by their excellent records we also used a similar stethoscopic bell. Apparatus was specially designed by one of us (WMR) to meet the peculiar requirements of direct phonocardiography. A direct recording technic was developed and applied to a series of dogs under experimental conditions. Since the tracings obtained were uniformly satisfactory, the method was transferred to the operating room and employed at surgical exploration of human patients having congenital or acquired heart disease.

Our present work is chiefly concerned with sounds and murmurs produced by the pulmonary valve. An experimental approach was therefore chosen in order to eliminate the sound due to the presence and function of this valve.

Heart sounds were recorded from the chest wall before opening the thorax. Direct recordings were made from the surface of the 4 chambers of the heart, the aorta and the pulmonary artery in a series of 20 adult dogs of 11 to 19 Kg. body weight. Fourteen of the 20 animals were operated on with the aid of extracorporeal circulation for various studies, most of them unrelated to the present communication.

Pulmonary stenosis was created surgically in 2 dogs by suture of 2 leaflets of the pulmonary valve through an incision in the pulmonary artery. Direct recordings were made before and after this operation. Then the incision was reopened in 1 dog and the entire pulmonary valve excised and postoperative phonocardiograms obtained.

The other dogs were operated on without the aid of extracorporeal circulation. This

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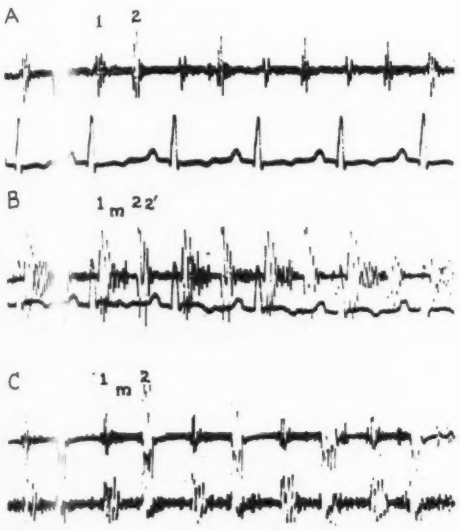


FIG. 1. *A*. Normal dog. Chest wall phonocardiograms from the pulmonary area and lead II electrocardiogram. *B*. Direct recording over the pulmonary valve. Note systolic murmur (*m*) and the split second sound (*2* and *2'*) lead II electrocardiogram. *C*. Simultaneous records from the pulmonary artery (*top*) and aorta.

group received Nembutal anesthesia 30 mg. per Kg. body weight. In 4 dogs the pulmonary valve was excised during venous inflow occlusion. After the azygos vein was ligated and the superior and inferior vena cavae occluded by means of umbilical tape, the 3 leaflets of the pulmonary valve were excised, through an incision in the right ventricular outflow tract, with forceps and scissors. The inflow occlusion lasted 1 to 2 minutes. Pre- and postoperative recordings were obtained. Each operation was performed as an acute experiment and the specimen examined. In all animals the pulmonary leaflets were completely removed down to their origin and no free remnants were found. The heart in which a pulmonary stenosis was created and the valve left in place was also examined and the valve found to be competent.

RESULTS

Sounds recorded from the surface of the heart and great vessels showed variations in

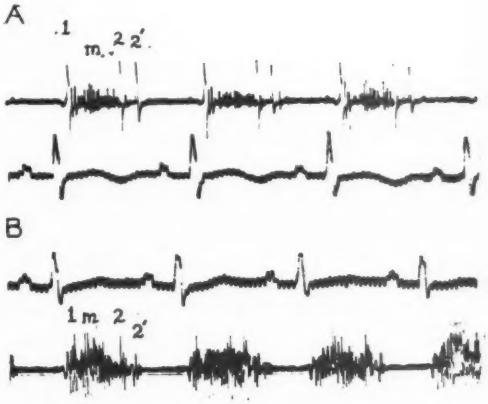


FIG. 2. *A*. Direct recording from over the pulmonary valve in a normal dog. Note physiologic systolic murmurs (*m*) and split second sound (*2* and *2'*). *B*. Postoperative record of surgically created pulmonary stenosis in same dog. Stenosis murmur is greater in amplitude and duration. *2'* is reduced in amplitude.

appearance according to the particular area from which they were recorded. The first heart sounds showed relatively the highest amplitude and greatest differentiation when they were obtained from a region overlying the mitral or tricuspid valve, and from over the atria where atrial sounds were also well recorded.

The second heart sound showed the highest amplitude and greatest differentiation when recorded from the aorta or pulmonary artery. Over the aorta the second sound was single, high pitched, of high amplitude and short duration. The second sound over the pulmonary artery was either completely or incompletely split. When splitting was incomplete, that is, when there was a long group of continuous vibrations, the beginning and the end of the group was of higher amplitude, whereas the amplitude was diminished in the middle (fig. 1). Simultaneous tracings from aorta and pulmonary artery showed that the second part of the sound was usually absent in the aortic tracing. Occasionally, however, a small vibration could be recorded from the aorta coinciding with the second part of the sound that was present over the pulmonary artery. Amplitude of the second sound and

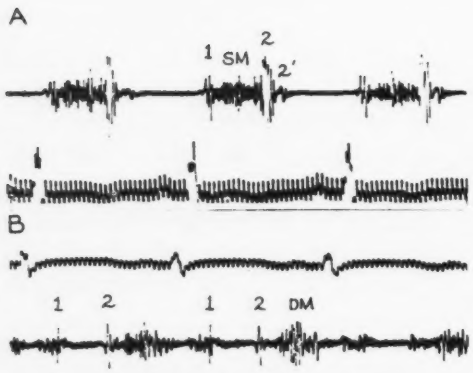


FIG. 3. *A*. Pulmonary stenosis. Note systolic murmur and reduction of second component ($2'$) of split second sound. *B*. After excision of pulmonary valve. Note elimination of systolic murmur (m) and of ($2'$) and appearance of diastolic murmur (*D.M.*).

degree of splitting varied considerably within the same animal. Generally the splitting was confined to the right ventricular outflow tract, the pulmonary valve area, where it was most marked, and the base of the vessel itself. Occasionally it was transmitted to the right ventricle and both atria.

A systolic murmur was found over the right ventricular outflow tract and the pulmonary artery (figs. 1 and 2). When the murmur was loud it showed a peak in midsystole. After creation of pulmonary stenosis, the murmur increased in amplitude and duration and extended across the aortic closure sound (figs. 2 and 3). After removal of the pulmonary valve, the first part of the second sound remained unchanged, whereas the second component disappeared. The systolic murmur also disappeared in every case and a low intensity crescendo-decrescendo diastolic murmur was found, starting at the place of the eliminated sound (fig. 3).

Since the method employed in experimental animals proved to be adequate and informative, it was subsequently applied to human patients subjected to closed and open heart surgery. The receiving bell used in human patients was the same size and shape as the one employed in the experiments, except that the suction groove was eliminated. The larger size of the hearts of human patients and the

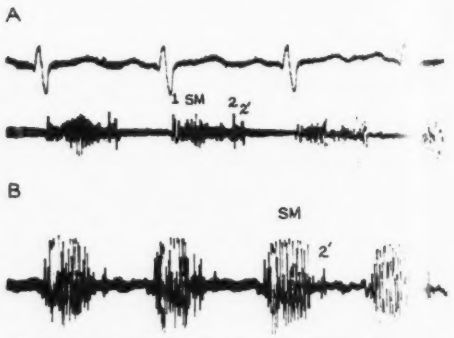


FIG. 4. *A*. Chest wall phonocardiogram from [illegible]rth left intercostal space of a 3½ year old girl [illegible]h a coexisting atrial and ventricular septal defect. Note delay of $2'$. *B*. Direct recording from the surf[illegible]e of right ventricle where the thrill produced by the [illegible]pact of the left-to-right interventricular jet, and th[illegible] murmur were maximal. The murmur begins with [illegible]itral closure and ends with aortic closure typical [illegible] the I.V.D. Wide splitting of the second sound is typical of the I.A.D.

comparatively slow heart rates did not require special attachments. Careful holding of the receiving bell was sufficient to give clear tracings without artifacts. This is true also for infants, particularly with cardiac enlargement. Thus it was possible to avoid injurious effects of suction. As direct recording in human patients is in an early stage and the number of cases studied is small, we refrain from any further communication at the present time, however, an example is shown in order to demonstrate the potentialities of the method. Figure 4*A* shows a chest wall tracing from a young girl with coexisting atrial and ventricular septal defects. The tracing obtained from the fourth left intercostal space at the sternal border is compared with one recorded from the right ventricular surface, where the murmur was loudest. It can be seen that the murmur in the direct tracing is pansystolic and stops at the aortic sound (fig. 4*B*). The wide splitting of the second sound is typical of an atrial defect.

DISCUSSION

A split second sound in experimentally [illegible]roduced bundle-branch block was demonstr[illegible]ed by Braun-Menéndez and Solari.[3] Wolf[illegible]th and Margolies[4] found in human cases [illegible]th

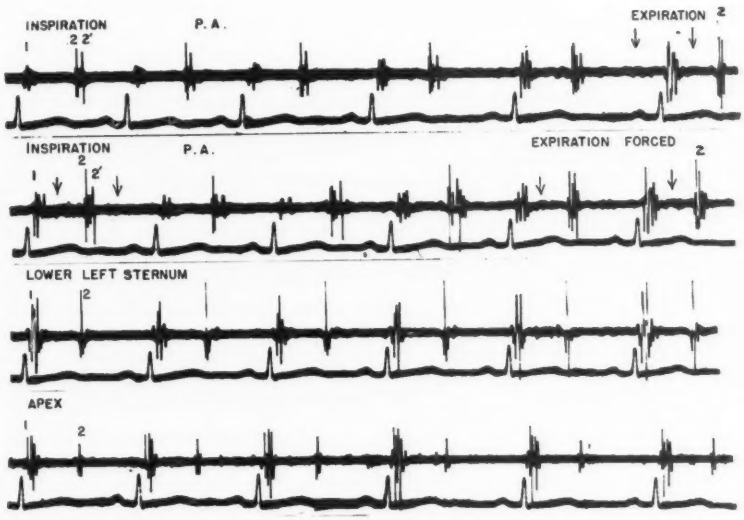


FIG. 5. Phonocardiogram from chest wall of a normal young adult. In the pulmonary area wide splitting of the second sound occurs on forced inspiration and decreases to fusion on forced expiration. The first component of the split coincides with aortic closure over the lower left sternum and apex.

bundle-branch block, that one component of the split second sound was aortic, the other pulmonary in origin. Leatham,[5] by means of simultaneous tracing from pulmonary, mitral, and aortic areas, arrived at the conclusion that the first part of a normally split second sound is aortic since it is synchronous with the dicrotic notch in carotid pulse tracings and the second is related to pulmonary valve closure. He stated that a split second sound is a persistent auscultatory finding in children and young adults. In our series of 30 young adults, only 5 failed to show it. The degree of splitting varied with respiration, being greatest in forced inspiration. In forced expiration it decreased to the point of fusion with the first component which always coincides with the aortic closure in other areas (fig. 5).

Bertrand, Milne, and Hornick[2] found, by direct phonocardiography, a split second sound in 4 of 23 normal dogs. As the splitting was confined to the tracings from the pulmonary artery, they have asked whether it represents aortic and pulmonary valve closure the first part being pulmonary valve closure, or whether both components are pulmonary in origin. In our tracings, splitting of the second sound, or at least recognizable sequence of 2 sounds, was a persistent finding. While the first component of the sound remained constant in amplitude within the same animal and was recorded from the aorta as well as the pulmonary artery, the second component was rarely found in the aortic tracing and in those cases only as small vibrations. After removal of the entire pulmonary valve, the second component disappeared whereas the first component remained unchanged. A diastolic murmur, obviously due to pulmonary insufficiency, appeared at the time the second component of the split sound had previously occurred. This seems sufficient evidence to justify the opinion that the second part of a normally split second sound is solely due to closure of the pulmonary valve, whereas it has no part in the first component. The aortic valve sound is transmitted to the pulmonary artery in its full amplitude, while only little of a pulmonary valve sound can be picked up from the aorta. Although the pulmonary valve is ordinarily located quite close to the chest wall, a single sound heard in the second or third left intercostal space at auscultation can not be interpreted

as necessarily pulmonary in origin, even though it may be louder than the second sound heard at the aortic area.

The systolic murmur heard over the pulmonary artery disappeared in every instance after removal of the pulmonary valve. Therefore, it can be no artifact, such as could be caused by compression of the thin walled vessel. It is known that a faint systolic murmur can frequently be heard in the pulmonary area of healthy children.[6] It is thought that this is caused by the rapid flow rate through a relatively narrow pulmonary orifice. The similarity of such a murmur with the findings in the dogs is striking. The fact that the murmur in dogs disappeared with removal of the pulmonary valve suggests that flow through the pulmonary orifice is not the only causative factor of such a murmur. It appears that the valve leaflets play an important role in the creation of this functional murmur. Chisholm[7] explains systolic murmurs associated with structurally normal pulmonary valves on the basis of physical changes in the valve cusps in relation to the lumen of the vessel, a process he termed "trigonoidation."

REFERENCES

1. Wiggers, C. J., and Dean, A. L., Jr. The nature and time relations of the fund mental heart sounds. Am. J. Physiol. 42 476, 1917.
2. Bertrand, C. A., Milne, I. G., and Ho ick, R.: A study of heart sounds and mu urs by direct heart recordings. Circulatio 13: 49, 1956.
3. Braun-Menéndez, E., and Solari, I A.: Asinoronismo ventricular per sección las ramas del has de His. I. Seccion la rama derecha. Rev. Soc. argent. bio 12: 331, 1936.
4. Wolferth, C. C., and Margolies, A.: synchronism in contraction of the ventri s in the so-called common type of bundle b nch block; its bearing on the determinat n of the side of the significant lesion and on the mechanism of split first and second sounds. Am. Heart J. 10: 425, 1935.
5. Leatham, A.: Splitting of the first and second heart sounds. Lancet 11: 607, 1954.
6. Mannheimer, E.: Phonocardiography in children. *In* Advances in Pediatries, Levine, S. Z., ed., Chicago, Year Book Publishers, 1955, vol. 7, p. 171.
7. Chisholm, D. R.: Trigonoidation of the semilunar valves and its relationship to certain basal systolic murmurs. Am. Heart J. 13: 362, 1937.

Correlation of Heart Sounds with Ejection Dynamics of The Right Ventricle

By A. Calhoun Witham, M.D.

The question is raised whether prolongation of right ventricular systole in atrial septal defect is the result of elevation of pulmonary systolic pressure and depression of pulmonary diastolic pressure. Data possibly supporting this view are presented.* The lack of comparable splitting of the second sound in ventricular septal defect may be the result of the absence of a comparable situation with reference to pulmonary systolic and diastolic pressures.

A poor correlation between right ventricular pressure and delay of the pulmonary closure sound in pure pulmonary stenosis was observed, contrary to the findings of Leatham and Weitzman.[1] However, other variables, such as a wide age range and wide spread of heart rates (from 58 to 150 per minute) at the time of right heart catheterization may have clouded the correlation.

*Ed.: Despite demonstrable correlation of the ratio of pulmonary systolic and diastolic pressures with the degree of splitting of the second sound the proximal cause of prolongation of right ventricular systole may be increased in the right ventricular stroke volume.

REFERENCE

1. Leatham, A., and Weitzman, D.: Auscultatory and phonocardiographic signs of pulmonary stenosis. Brit. Heart J. **19**: 303, 1957.

Mechanisms of Fixed Splitting of the Second Heart Sound

By JOSEPH K. PERLOFF, M.D. AND W. PROCTOR HARVEY, M.D.

PROPER clinical analysis of the second heart sound has only recently been emphasized.[1] An understanding of the normal second heart sound has increased the diagnostic usefulness of its variations in congenital and acquired heart disease. In atrial septal defect, as emphasized by Wood,[6] the aortic and pulmonic components of the second heart sound are not only widely separated, but the split remains fixed throughout the respiratory cycle. The following study was designed to investigate the physiology of fixed splitting of the second heart sound in atrial septal defect and in 3 other categories in which this phenomenon has been observed—right and left bundle-branch block with right ventricular failure, and mitral insufficiency with right ventricular failure.

MATERIALS AND METHODS

A total of 69 cases were studied. They consisted of 25 normal controls, 13 patients with atrial septal defect, 10 with pure mitral insufficiency, 11 with right bundle-branch block, and 10 with left bundle-branch block. The material included patients in the Georgetown University Medical Center and in the Clinic of Surgery, National Heart Institute, Bethesda. All patients had electrocardiograms and chest fluoroscopy. In the group with atrial septal defect the diagnoses were established by right heart catheterization. The group with pure mitral insufficiency had left heart catheterization. The preoperative diagnosis of atrioventricularis communis was established by the additional use of dye dilution curves with the injections made into the left atrium and left ventricle.[2]

The patients with right and left bundle-branch block had congenital conduction defects (right), acquired conduction defects associated with arteriosclerotic heart disease, and one acquired (left) after closure of a large patent ductus arteriosus. The diagnoses of complete right and left bundle-branch block were made on the basis of the criteria of Wilson.[3] The criteria for the diagnosis of right ventricular failure were clinical and consisted of the presence of systemic venous hypertension, pitting peripheral edema, and congestive hepatomegaly.

The phonocardiograms were logarithmic[4] recordings at paper speeds of 50-75 mm. second, taken with either a standard twin-beam Sanborn or a specially built Cambridge with the same frequency response characteristics. Indirect carotid pulses were obtained with a light tambour applied to the neck. The interval between aortic valve closure and the inscription of the dicrotic notch of the carotid pulse varied 0.02 to 0.04 second, depending on where in the neck the carotid pick-up was located. The intracardiac pulses were, in certain instances, taken on a cathode ray photographic recorder. It is to be emphasized that all recorded events were appreciated by auscultation, and hence have direct clinical application.

RESULTS

Normal Controls. The majority were young adults, although the ages ranged from 5 to 50 years. During relaxed respiration the second heart sound varied from expiratory synchrony to inspiratory separation averaging 0.04 to 0.05 second. The younger subjects differed somewhat in that the second sound more often tended to remain slightly split during expiration (average 0.02 seconds) and tended to split more widely during inspiration. This expiratory asynchrony would often disappear if the subject expired more completely. When the respiratory excursions were increased in magnitude, splitting tended to become more pronounced in all ages, but especially in the younger subjects in whom the inspiratory asynchrony occasionally reached 0.08 to 0.09 seconds. When the records were taken during held expiration, held inspiration, or in the respiratory mid-position, the two components of the second sound tended to drift apart to varying degrees. It should be emphasized, therefore, that analysis of the second heart sound must be made during active respiration.

Supported in part by grants from the U.S. Public Health Service (H-3319), and the Washington Heart Association.

Atrial Septal Defect. Thirteen patients were studied before and after surgical closure of the defect. In each instance the surgeon was satisfied with the technical result of the procedure. Ten of the patients had the RSr'-type pattern[9] in the electrocardiogram and one patient had the pattern of complete right bundle-branch block.[3] The QRS configuration of all 13 tracings remained unchanged at the time the postoperative study was done. Eight of these patients were recatheterized postoperatively. By this evidence the defect had been closed in all.

In the preoperative phonocardiograms the splitting of the second heart sound remained fixed throughout respiration. In one patient not operated upon because the shunt was small (less than 1 L. per minute) and the right ventricle normal in size, the split widened 0.02 to 0.025 seconds during inspiration, but never achieved expiratory synchrony. Two patients had arrhythmias causing variations in cycle length, i.e., a wandering pacemaker in the sinoatrial node and episodes of sinus arrest. The split second sound widened after the longer cycle lengths and narrowed after the shorter cycle lengths.

In 11 of the 13 patients the second sound on the postoperative phonocardiogram split normally during inspiration and became single during expiration. In 1 of the 13, however, the second sound did not normalize. Preoperatively, the split had been 0.08 second. Postoperatively, the split was 0.06 second (comparing complexes of the same cycle length) and during inspiration the pulmonic component moved less than 0.02 second. There was no delay in the onset of the right ventricular pressure pulse in the postoperative catheterization study. There was no clinical evidence of right ventricular failure. Postoperative catheterization proved the defect to be closed. The explanation for the findings in this case is not apparent.

In the 1 patient with complete right bundle-branch block, the postoperative split of the second sound increased from an expiratory separation of 0.03 second to an inspiratory separation of 0.06 second. This can be considered a normal inspiratory delay in pulmonic valve closure. The relationship of the two components of the second sound is typical of complete right bundle-branch block. This is of further interest since the onset of the right ventricular pressure pulse was not delayed, occurring 0.06 second after the onset of the QRS of the electrocardiogram.[5]

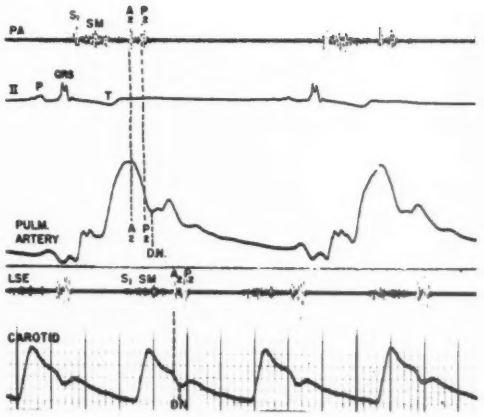


FIG. 1. Phonocardiograms with pulmonary and carotid arterial pulses in a patient with proven atrial septal defect. Note that in the upper tracing pulmonic valve closure (P_2) times with the dierotic notch (*D.N.*) of the pulmonary arterial pulse (interval between P_2 and *D.N.* accounted for by delay in transmission of pulse from pulmonic valve to catheter tip, plus instrumental delay), and note that in the lower tracing aortic valve closure (A_2) times with the dierotic notch of the carotid arterial pulse (interval between A_2 and *D.N.* accounted for by delay in transmission of pulse from aortic valve to carotid pick-up plus instrumental delay). *PA*, pulmonary area, S_1, first sound; *SM*, systolic murmur; *L.S.E.*, lower left sternal edge.

Complete Right Bundle-Branch Block. Eleven patients were studied. In the 8 with compensated right ventricles the split second sound widened on inspiration and narrowed on expiration but never became single. In the 3 patients with right ventricular failure, the split remained fixed throughout the respiratory cycle.

Complete Left Bundle-Branch Block. Ten patients were studied. In the 6 with compensated right ventricles, the second heart sound split during expiration and became

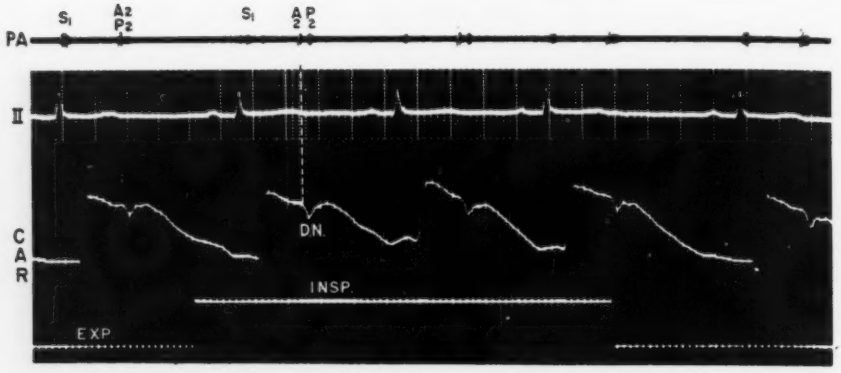


FIG. 2. Normal 22-year-old male medical student. Note that aortic (A_2) and pulmonic (P_2) components of the second sound are synchronous during expiration (*EXP.*) and split during inspiration (*INSP.*) *Car.*, carotid pulse.

single during inspiration. In the 4 patients with right ventricular failure, the second sound remained constantly split throughout the respiratory cycle.

Pure Mitral Insufficiency. Ten patients were studied. In the 6 with compensated right ventricles, the split second sound widened with inspiration and narrowed with expiration, but never became single. In the 4 patients with right ventricular failure, the split remained fixed. The width of the split varied from 0.04 to 0.10 second. None of these patients had the electrocardiographic pattern of right bundle-branch block.

DISCUSSION

As early as 1866, Potain[1] was aware that the second heart sound (S_2) split during the inspiratory phase of respiration. In 1950, Barber et al.[6] emphasized this finding in children. Leatham and Towers[7] subsequently confirmed its occurrence in the majority of healthy adults. The first component of the split is recorded at all valve areas and is synchronous with the dicrotic notch of the carotid pulse (fig. 1), a feature identifying it as the sound of aortic valve closure (A_2). The second component is normally confined to the pulmonary area or the immediately subjacent left sternal edge and is synchronous with the dicrotic notch of the pulmonary arterial pulse (fig. 1), a feature identifying it as the sound of pulmonary valve closure (P_2). During inspiration the effective *pulmonary* venous filling pressure remains unchanged, since pulmonary veins, left atrium, and left ventricle share equally the inspiratory fall in intrathoracic pressure. However, the effective *systemic* venous filling pressure increases with inspiration since the inspiratory pressure in the right heart falls below that of the extrathoracic great veins. This results in selective inspiratory augmentation of right-sided filling. The right ventricle takes longer to eject this increased volume and its prolonged ejection time is reflected in delayed pulmonary valve closure, giving rise to the normal inspiratory splitting of the second heart sound (fig. 2). It is to be emphasized that only P_2 moves with respiration, the timing of A_2 remaining unchanged.*

The phenomenon of fixed splitting of the second heart sound in atrial septal defect has been well documented.[8] Our observations confirm the findings that even with deep inspiration and expiration the interval between aortic and pulmonic components of the second heart sound in atrial septal defect remains constant or moves very slightly (less than 0.02 second), the sounds never becoming single (fig. 3*A*). In 1 patient with a proven os ium

*Ed.: Compare contradictory findings of Boyer and Chisholm in the succeeding paper.

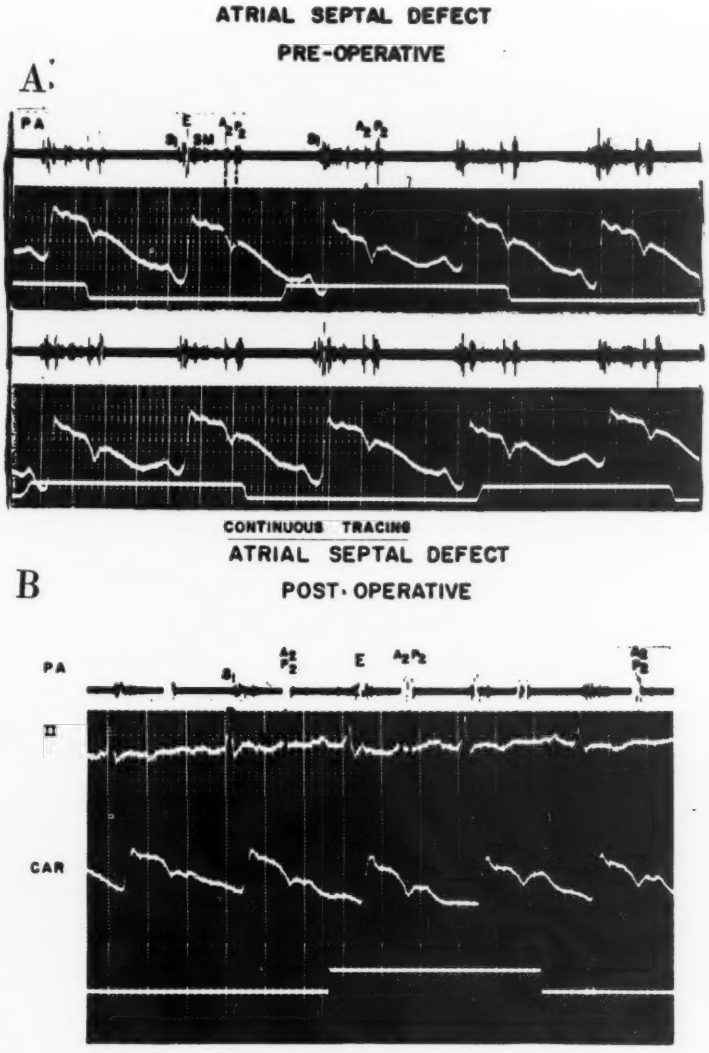


FIG. 3. *A.* Proven atrial septal defect, preoperative. Note that the interval between the aortic (A_2) and pulmonic (P_2) components of the second sound remains fixed throughout the respiratory cycle. *E*, pulmonic ejection sound. *B.* Same patient after surgery. The atrial septal defect was proven to be closed by postoperative cardiac catheterization. Note that now the aortic (A_2) and pulmonic (P_2) components of the second sound are synchronous during expiration and split normally during inspiration.

prim m defect and normal mitral and tricusp l valves, and in 1 patient with ostium prim m type of atrial septal defect with mitr l incompetence, fixed splitting of the secon l sound occurred. Pulmonary hypertensive atrial defects are exceptions to this rule and are not included in this study.

A basic hemodynamic expression of atrial septal defect is constant right-sided diastolic hypervolemia. The right ventricle apparently

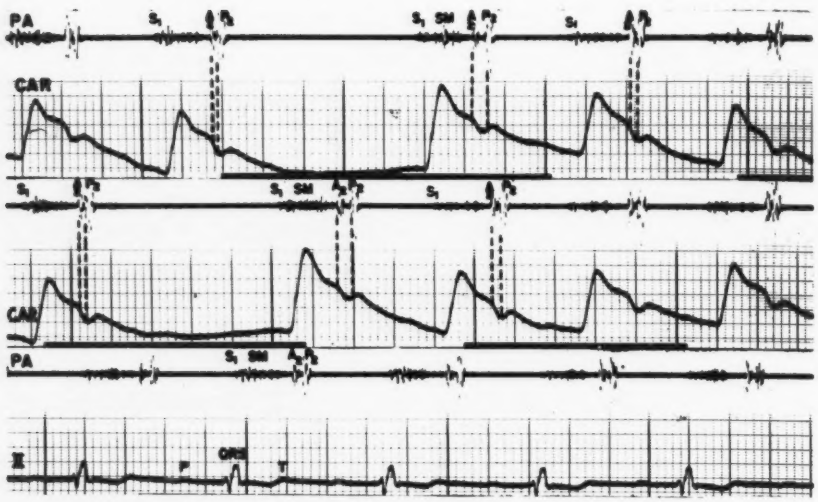


FIG. 4. Proven atrial septal defect, preoperative, with variations in cycle length due to episodes of sinus arrest. Note that after longer cycle lengths the interval between aortic (A_2) and pulmonic (P_2) components of the second sound increases. After shorter cycle lengths this interval decreases.

takes longer to eject this increased volume, hence, its stroke time is prolonged and the pulmonic valve closes later than the aortic (fig. 3*A*). Because the overfilled state is present throughout the respiratory cycle, the right ventricular volume during expiration may not diminish. Conversely, as a result of its already excessive diastolic inflow, the right ventricle apparently does not accept the additional inspiratory augmentation of filling, and its stroke volume thus does not increase during inspiration. The result is that aortic and pulmonic valve closures remain constantly separated, their interval being affected little, if at all, by respiration (fig. 3*A*).

That the asynchrony of semilunar valve closure is not a reflection of the electrocardiographic pattern of "incomplete right bundle-branch block"—perhaps better termed the RSr'-V_1 pattern[9]—was demonstrated by studying 12 patients with the ostium secundum type of atrial septal defect, and 1 with the ostium primum type before and after surgical repair of these lesions. As soon as the second sound could be analyzed (often the day after surgery), it was found to split normally during inspiration, and close during expiration (fig. 3*B*). In no instance was there any change in the QRS pattern when the postoperative study was made. One patient had complete right bundle-branch block and a fixed split before surgery. Postoperatively, the split widened with inspiration and narrowed with expiration, but never became single, reflecting the usual finding in complete right bundle-branch block (see below). A residual left-to-right shunt through anomalous pulmonary veins may result in a failure of the second sound to normalize postoperatively, even though the defect in the septum is closed.

The following observations suggest that, although the split second sound in atrial septal defect remains fixed relative to respiration, it may vary with changes in cycle length. Figure 4 illustrates an increase in the A_2-P_2 interval from 0.04 to 0.08 second coincident with an increase in cycle length caused by periods of sinus arrest. It can be seen that the interval between S_1 and A_2 remains constant, hence the increase in A_2-P_2 interval must have been due to further delay in

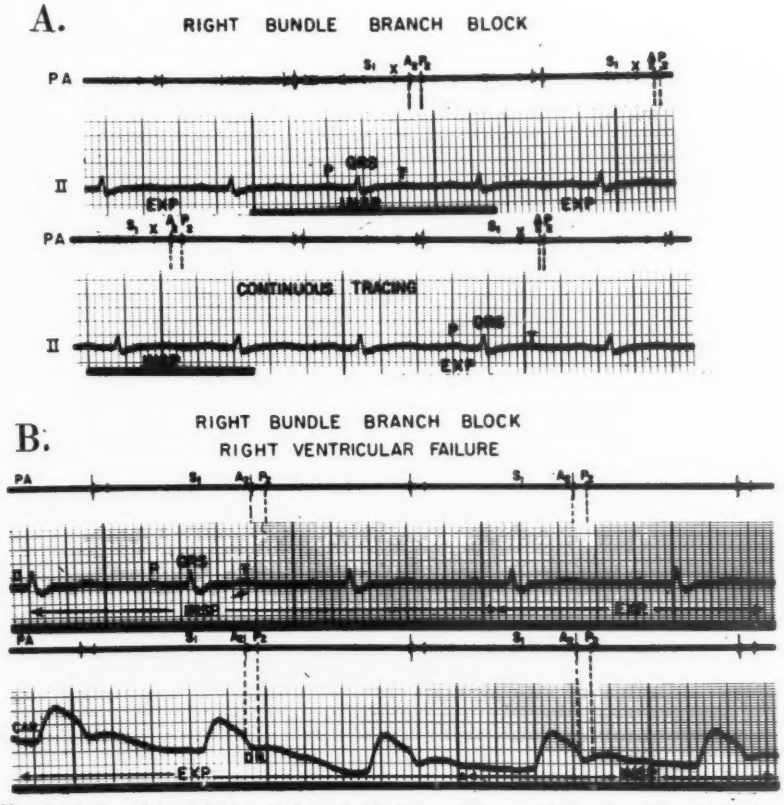


FIG. 5. *A.* Complete right bundle-branch block in a 60-year-old female with arteriosclerotic heart disease. Note that during inspiration the interval between aortic (A_2) and pulmonic (P_2) components of the second sound increases and during expiration the interval decreases, but the two sounds never become single. *X*, systolic cardiorespiratory click. *B.* Complete right bundle-branch block in a 58-year-old male with hemochromatosis and right ventricular failure. Note that the interval between aortic (A_2) and pulmonic (P_2) components of the second sound remains constant throughout the respiratory cycle. The first sound (S_1) is soft because of a prolonged P-R interval.

monic valve closure, reflecting a prolongation of right ventricular stroke time. Thus, after a long cycle length the right ventricular stroke time selectively lengthens. The same phenomenon was observed in another patient with an atrial septal defect, in which the cycle length varied because of a wandering pacemaker in the sinoatrial node. These events might be explained in the following fashion. When there is a defect in the atrial septum all 4 cardiac chambers are in common communication during diastole, but the rate of flow into the right ventricle far exceeds the rate of flow into the left ventricle. An increase in the diastolic filling period should therefore contribute disproportionately to *right* rather than to *left* ventricular filling. With longer cycle lengths it is postulated that the right ventricle may be the principle, if not the exclusive recipient of the added increment of diastolic filling. This should reflect itself in selective prolongation of right ventricular stroke time, delay in pulmonic valve closure and wider separation of the A_2-P_2 interval during the longer cycle lengths.

Fixed splitting of the second heart sound

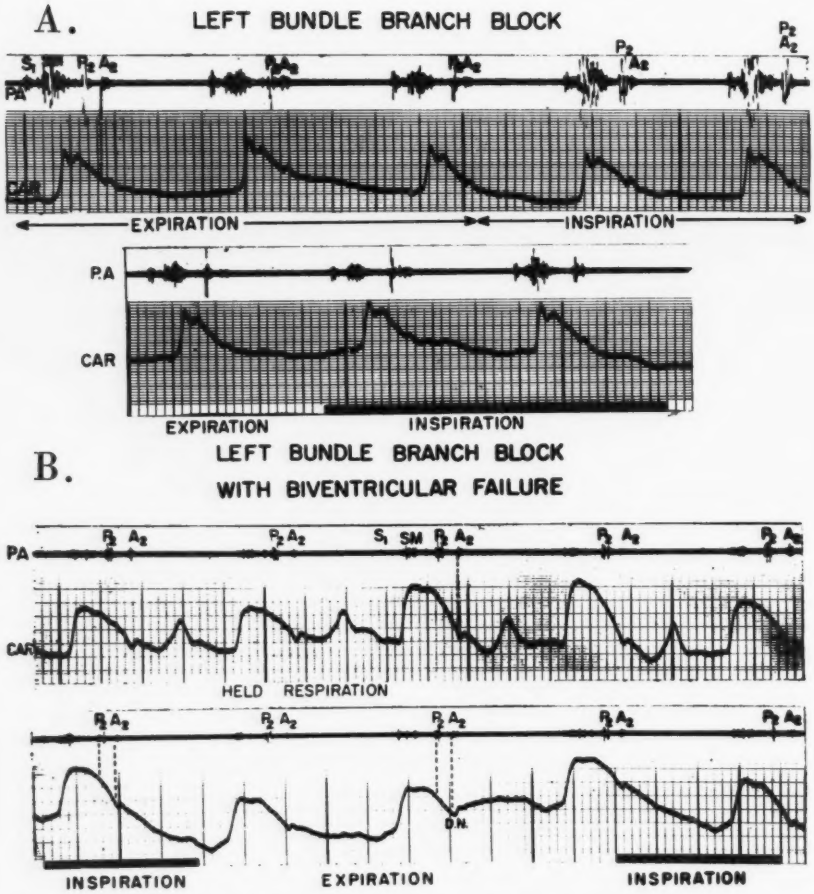


FIG. 6. *A*. Complete left bundle-branch block acquired after surgical closure of a large patent ductus arteriosus in a 37-year-old female. Note that the aortic (A_2) component of the second sound falls *after* the pulmonic (P_2) component of the second sound. Hence during *inspiration* the second sound is single and during expiration the second sound is split. *B*. Complete left bundle-branch block in a 72-year-old white female with arteriosclerotic heart disease and heart failure. Note that the inspiratory delay in pulmonic (P_2) valve closure does not occur, hence the second sound remains split throughout the respiratory cycle.

is, therefore, a valuable diagnostic sign of atrial septal defect, and possibly of the atrioventricularis communis type of anomaly. This phenomenon is probably a manifestation of the right-sided diastolic hypervolemia, which prevents the right ventricle from undergoing its normal respiratory changes in stroke volume. The rather prompt return to the normal state after the defect is closed supports this concept.

OTHER OBSERVATIONS

Although heretofore fixed splitting of the second heart sound has been described only in atrial septal defect, the following considerations led us to postulate its occurrence in other conditions. If the right ventricle in a state of failure were operating on the plateaus of its Starling curve, it should not be able to convert the inspiratory augmentation of filling into increased stroke volum

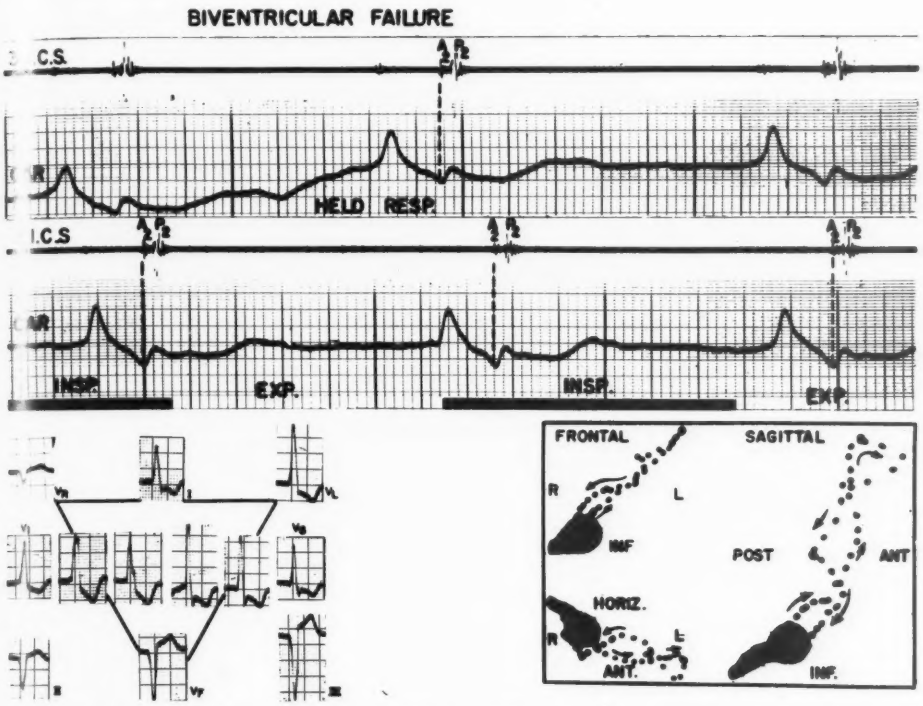
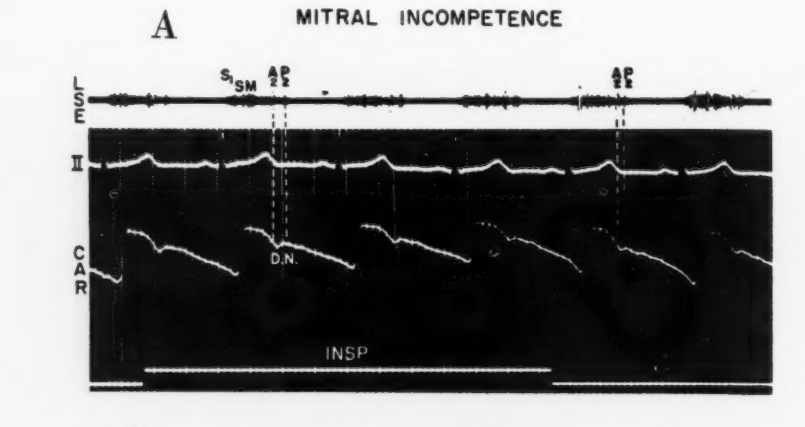


FIG. 7. Biventricular conduction defects in a 62-year-old male with hypertensive-arteriosclerotic heart disease and right ventricular failure. Note that in the phonocardiograms (*upper pair of tracings*) the initial component of the split second sound times with the dicrotic notch of the synchronous carotid (*CAR*) pulse, thus establishing the normal sequence of semilunar valve closure. In the scalar electrocardiogram (*lower left*) the limb lead suggest complete left bundle-branch block and the precordial leads suggest complete right bundle-branch block. The vectorcardiogram (*lower right*) reveals biventricular conduction defects. 3 I.C.S., third left intercostal space.

Hence, in this state of failure, the right ventricle might be expected to have a constant ejection time throughout the respiratory cycle, resulting in a disappearance of the normal inspiratory delay in pulmonic valve closure. This thesis was tested in 3 categories of patients with sufficient splitting of the second heart sound to allow detailed analysis.

The *first group* consisted of patients with complete right bundle-branch block. A commonly observed mechanical sequel of this delay in right ventricular depolarization is a delay in pulmonic valve closure. This reflects itself in abnormally wide splitting of the second heart sound,[1] which fails to become single during expiration. During inspiration the normal augmentation of right-sided filling still occurs with the associated delay in pulmonary valve closure. One finds accordingly that although the aortic and pulmonic components of the second sound widen their interval during inspiration and narrow it during expiration, they fail to become synchronous during the expiratory phase of respiration (fig. 5*A*). However, when right bundle-branch block occurs in the presence of right ventricular failure, the splitting of the second sound remains fixed (fig. 5*B*). This is believed due to the inability of the failing right ventricle to convert its inspiratory augmentation of filling into increased stroke volume. As a consequence of this inability, the inspiratory delay in pulmonary valve closure should



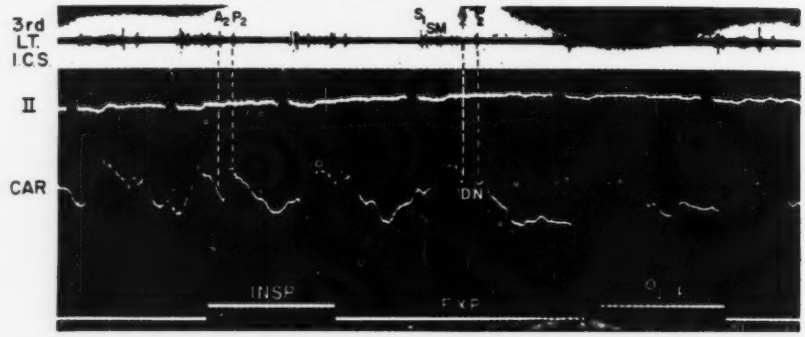


FIG. 8. *A*. Pure rheumatic mitral incompetence in a 28-year-old female. Note that although the interval between aortic (A_2) and pulmonic (P_2) components of the second sound widens with inspiration and narrows with expiration, the 2 components never become single. *B*. Pure rheumatic mitral incompetence in a 23-year-old white female with associated right ventricular failure. Note that the second sound is not only widely split, but the interval between aortic (A_2) and pulmonic (P_2) components remains fixed throughout the respiratory cycle. 3rd LT. I.C.S., third left intercostal space.

not occur. The A_2-P_2 interval would, therefore, remain unchanged.

The *second group* consisted of patients with left bundle-branch block. It appears that a mechanical sequel of this delay in left ventricular depolarization is an associated delay in aortic valve closure. The delay is usually sufficient to cause the aortic valve to close after the pulmonic, thus reversing the normal closing sequence of the semilunar valves. This is demonstrated by timing A_2 with the dicrotic notch of the carotid pulse (fig. 6*A*). The result of this "paradoxical splitting" of the second heart sound[11] is expiratory separation of its two components. During inspiration the timing of pulmonary valve closure moves toward aortic closure and the second sound thus becomes single (fig. 6*A*). However, in the presence of right ventricular failure, S_2 does *not* become single during inspiration because the inspiratory delay in pulmonic valve closure does not occur (fig. 6*B*). This results in fixed splitting of the second heart sound in left bundle-branch block.

In one case this method of analysis was of particular interest. The patient, a 57-ye-

old male with hypertensive-arteriosclerotic heart disease had an electrocardiogram which resembled left bundle-branch block in the limb leads, and right bundle-branch block in the precordial leads. The vectorcardiogram using the Schmidt-Simonson system[12] suggested bifascicular conduction defects. This apparent electrocardiographic paradox has been variously interpreted. Some investigators[13] consider these tracings examples of right bundle-branch block, emphasizing the unreliability of the limb leads in distinguishing the site of the block. Others[14] feel that in some cases this pattern should be regarded as left bundle-branch block with extensive posterolateral myocardial infarction. Auscultatory examination of the patient disclosed a widely split second heart sound, but since marked right ventricular failure was present the split remained fixed, and therefore, could not be used to distinguish right from left bundle-branch block. The phonocardiogram with synchronous carotid arterial pulse (fig. 7) revealed a normal sequence of aortic-pulmonic valve closures, suggesting in this instance the *mechanical* asynchrony of a right bundle-branch block. These observations further illustrate that in the presence of right ventricular failure, one cannot distinguish right from left bundle-branch block by auscultation.

The *third group* consisted of patients with pure mitral insufficiency associated with wide splitting of the second heart sound. Unusually wide splitting of the second sound has been observed in this lesion[15] and attributed to premature aortic valve closure. It is suggested that if the left ventricle can expel its contents not only into the systemic circulation but also into the left atrium, then its ejection time might be shortened, resulting in early aortic valve closure. If this is sufficiently pronounced, aortic and pulmonic valve closures may remain constantly separated (fig. 8*A*). It is to be noted, however, that—as in normals—inspiratory prolongation of right ventricular ejection time still occurs, resulting in inspiratory delay of pulmonic valve closure and *increased* splitting of the second heart sound (fig. 8*A*). It was found, however, that when the right ventricle decompensates in the presence of mitral insufficiency with wide splitting of the second heart sound, there is no inspiratory delay in pulmonic valve closure, hence, the split becomes fixed (fig. 8*B*).

These data do not permit conclusions regarding the state of decompensation at which the inspiratory delay in pulmonic valve closure would fail to occur. The severity of right ventricular failure will vary from time to time and from case to case. Even if the failing ventricle is operating on a depressed function curve, it still may be able to increase its stroke work if it has not yet reached the plateau of the curve.[10] It might be anticipated, therefore, that not all patients in whom right ventricular failure coexists with complete bundle-branch block or mitral insufficiency will illustrate the phenomenon of fixed splitting of the second heart sound.

Summary

Forty-four patients with wide splitting of the second heart sound and 25 normal controls were studied with fast speed logarithmic phonocardiograms.

In the control group, inspiratory augmentation of right heart filling increased the right ventricular stroke volume, prolonged the right ventricular stroke time and delayed pulmonic valve closure, thus altering the second sound from expiratory synchrony to inspiratory separation of its 2 components.

In the group with atrial septal defects, the second sound normalized postoperatively, reflecting the ability of the right ventricle to undergo its normal inspiratory increase and expiratory decrease in stroke volume when the defect was closed. Before closure, the right ventricular stroke time neither shortened with expiration nor lengthened with inspiration because of the constant diastolic right ventricular hypervolemia. Hence, preoperatively the interval between aortic and pulmonic valve closures remained characteristically wide and fixed. That the preoperative delay in pulmonic valve closure could

not have been a reflection of "incomplete right bundle-branch block" was illustrated by the postoperative normalization of the second sound without change in the QRS pattern of the electrocardiogram. Although the split of the second sound was not altered by respiration, it was altered by change in cycle length, widening after longer cycles and narrowing after shorter cycles.

Wide splitting of the second heart sound was found in mitral insufficiency because of early aortic valve closure, in complete right bundle-branch block because of delayed pulmonic valve closure, and in complete left bundle-branch block because of a reversed sequence of aortic-pulmonic valve closure. When right ventricular failure coexisted with these lesions, the decompensated chamber did not convert its inspiratory augmentation of filling into increased stroke volume. The inspiratory increase in right ventricular stroke time and the inspiratory delay in pulmonic valve closure therefore could not occur so the split of the second sound remained fixed throughout the respiratory cycle.

Acknowledgment

The authors acknowledge with pleasure the freedom with which we were allowed to study the cases on Services of Dr. Andrew G. Morrow and Dr. Robert P. Grant at the National Heart Institute, Bethesda, and of Dr. Charles A. Hufnagel at the Georgetown University Medical Center, Washington, D. C. We are further indebted to Dr. Hubert V. Pipberger for taking and interpreting the vectorcardiograms.

Summario in Interlingua

Quaranta-quatro patientes con large fission del secunde sono cardiac 25 normal subjectos de controlo esseva studiate per medio de phonocardiogrammas logarithmic a grande velocitate.

In le gruppo de controlo, augmentation inspiratori del replenamento dextero-cardiac augmentava le volumine per pulso dextero-ventricular, prolongava le tempore del pulso dextero-ventricular, e retardava le clausion del valvula pulmonic, de maniera que le secunde sono esseva alterate ab synchronia e piratori a separation inspiratori de su 2 c mponentes.

In le gruppo de patientes con defect s del septo atrial, le secunde sono se norma sava post le operation. Isto reflecteva le cap itate del ventriculo dextere de experientiar s nor-mal augmento inspiratori e diminution xpi-ratori in le volumine per pulso quando defecto esseva claudite. Ante le clausi , le tempore per pulso dextero-ventricular n se reduceva in expiration e non se prolo gava in inspiration a causa del constante di tolic hypervolemia dextero-ventricular. Per nse-quente, ante le operation le intervallo in r le clausion del valvula aortic e illo del valvula pulmonic remaneva characteristicamente large e fixe. Le facto que le retardo pre-operatori in le clausion del valvula pulmonic non poteva esser un reflexion de "incomplete bloco de branca dextere" esseva demonstrate per le normalisation post-operatori del sono que occurreva sin alteration in le formation de QRS in le electrocardiogramma. Ben que le fission del secunde sono non esseva alterate per le respiration, un alteration de illo occurreva como effecto de alterationes del longor de cyclo: illo deveniva plus large post cyclos prolongate e plus restringite post cyclos accurtate.

Large fissiones del secunde sono cardiac esseva trovate in insufficientia mitral a causa de precoce clausion del valvula aortic, in complete bloco de branca dextere a causa del retardate clausion del valvula pulmonic, e in complete bloco de branca sinistre a causa de reversion del sequentia aortic-pulmonic in le clausiones valvular. In casos in que disfallimento dextero-ventricular co-existeva con iste lesiones, le camera discompensate non converteva su augmentation inspiratori del replenamento in un augmento del volumine per pulso. Le augmento inspiratori del tempor del pulso dextero-ventricular e le retardo ins iratori del clausion del valvula pulmonic no poteva, per consequente, occurrer. Le fissio del secunde sono remaneva fixe durante le mplete cyclo respiratori.

REFERENCES

1. LEATHAM, A.: Splitting of the first and second heart sounds. Lancet **2**: 607, 1954.
2. BRAUNWALD, E., TANENBAUM, H., AND MORROW, A. G.: Dye-dilution curves from left heart and aorta for localization of left-to-right shunts and detection of valvular insufficiency. Proc. Soc. Exper. Biol. & Med. **94**: 510, 1957.
3. WILSON, F. N., ROSENBAUM, F. F., AND JOHNSTON, F. D.: Interpretation of the ventricular complex of the electrocardiogram. Advances Int. Med. **2**: 1, 1947.
4. LIPPAPORT, M. B., AND SPRAGUE, H. B.: Graphic registration of the normal heart sounds. Am. Heart J. **23**: 591, 1947.
5. BRAUNWALD, E., AND MORROW, A. G.: Sequence of ventricular contraction in human bundle branch block. Am. J. Med. **23**: 205, 1957.
6. BARBER, J. M., MADIGSON, O., AND WOOD, P.: Atrial septal defect. Brit. Heart J. **12**: 277, 1950.
7. LEATHAM, A., AND TOWERS, M.: Splitting of the second heart sound in health. Brit. Heart J. **13**: 575, 1951.
8. —, AND GRAY, I.: Auscultatory and phonocardiographic signs of atrial septal defect. Brit. Heart J. **18**: 193, 1956.
9. BLOUNT, S. G., MUNYAN, E. A., AND HOFFMAN, M. S.: Hypertrophy of the right ventricular outflow tract. A concept of the electrocardiographic findings in atrial septal defect. Am. J. Med. **22**: 784, 1957.
10. SARNOFF, S. J.: Myocardial contractility as described by ventricular function curves, observations on Starling's law of the heart. Physiol. Rev. **35**: 107, 1955.
11. GRAY, I.: Paradoxical splitting of the second heart sound. Brit. Heart J. **18**: 21, 1956.
12. SCHMITT, O. H., AND SIMONSON, E.: Symposium on electrocardiography and vectorcardiography. Arch. Int. Med. **96**: 574, 1955.
13. JONES, A. M., AND FEIL, H.: The effect of posture upon axis deviation in human bundle block. Am. Heart J. **36**: 739, 1948.
14. RICHMAN, J. L., AND WOLFF, L.: Left bundle branch block masquerading as right bundle branch block. Am. Heart J. **47**: 383, 1954.
15. BRIGDEN, W., AND LEATHAM, A.: Mitral incompetence. Brit. Heart J. **15**: 55, 1953.

Physiologic Splitting of the Second Heart Sound

By Samuel H. Boyer, M.D., and Arthur W. Chisholm, M.D.

An increase in the magnitude of splitting of the 2 components of the second heart sound, as heard in the pulmonary area during inspiration, has been recognized for nearly a century.[1] Recent reports[2, 3] suggest that this phenomenon is due to a relative delay of pulmonary valve closure when the increased venous return during inspiration causes prolongation of right ventricular mechanical systole. However, it seems reasonable from physiologic studies[4, 5] that inspiratory shortening of left venstricular systole, resulting in an earlier aortic closure sound, could contribute to the splitting. Indeed, figure Q of a review by Leatham[6] suggests some contribution from movement of the aortic component.

In order to test this hypothesis heart sound recordings were obtained from young normal subjects with easily perceptible second heart splitting. For purposes of measurement the first sound and second sound components were required to have early fast deflections which were reasonably constant in form throughout respiration. Twenty persons were found who fulfilled these criteria. Precordial recordings were simultaneously obtained from the apex and an area of the base which allowed the greatest discrimination of second sound components. Signals from Altec capacitor microphones, electrocardiograms and pneumogram were recorded on a Hathaway oscillograph, (model S-14C), at a paper speed of 100 mm. per second.

The intervals between the first heart sound and the first (aortic) component of the second sound (1-2A) and the interval from the first sound to the second (pulmonary) component of the second sound (1-2 P) were measured with an accuracy of ± 3 msec. Changes in these intervals were calculated for each of at least 3 consecutive respiratory cycles.

The mean change of all the 1-2 A intervals during a respiratory cycle was 11.7 msec. while that of the 1-2 P was 11.4 msec.

Such changes were always opposite in sign. Thus early aortic valve closure contributes as much as delayed pulmonic valve closure to the maximal second sound splitting of in-

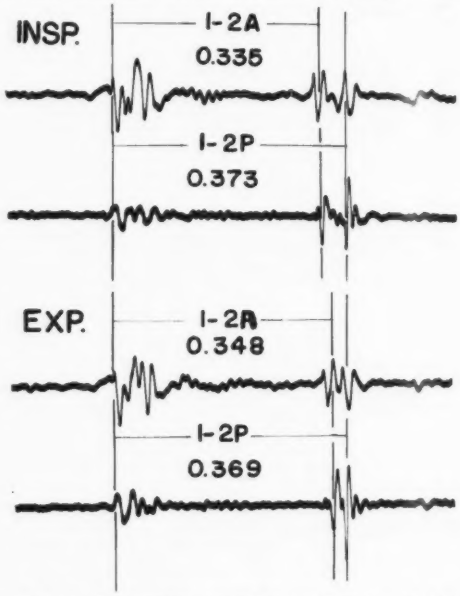


Fig. 1. Respiratory variation in duration of 1-2A and 1-2P.

spiration. Similarly, the reason that splitting is minimal in expiration is that aortic closure is delayed and pulmonic closure occurs early. In the example shown in figure 1 the variation of the 1-2 A, 13 msec., actually exceeds that of the 1-2 P which is only 4 msec.

We believe that this method may be a fruitful one for studying abnormal relationships between the 2 ventricles, as in atrial septal defect.

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REFERENCES

1. P[illegible]AIN, P.—C. E.: Note sur les dédoublements [illegible]rmaux des bruits de coeur. Bull. et mém. [illegible]c. méd. hôp. Paris **3** (2nd series): 138-[illegible]8, 1866.
2. L[illegible]THAM, A.: Splitting of the first and sec[illegible]d heart sounds. Lancet **2**: 607, 1954.
3. G[illegible]Y, I. R.: Paradoxical splitting of the sec[illegible]d heart sound. Brit. Heart J. **18**: 21, [illegible]56.
4. SHULER, R. H., ENSOR, C., GUNNING, R. E., MOSS, W. G., AND JOHNSON, V.: The differential effects of respiration on the left and right ventricles. Am. J. Physiol. **137**: 620, 1942.
5. LAUSON, H. D., BLOOMFIELD, R. A., AND COURNAND, A.: The influence of the respiration on the circulation in man. Am. J. Med. **1**: 315, 1946.
6. LEATHAM, A.: Phonocardiography. Brit. Med. Bull. **8**: 333, 1952.

The Tricuspid Component of the First Heart Sound in Mitral Stenosis

By HERBERT N. HULTGREN, M.D., AND THOMAS F. LEO, M.D.

IN MITRAL stenosis the pressure in the left ventricle during the initial portion of systole does not exceed the elevated pressure in the left atrium until 0.08 to 0.12 second after the onset of the QRS complex of the electrocardiogram. This is probably the most important factor responsible for the prolongation of the interval from the QRS onset to the sound of mitral closure in mitral valve disease, although the stiffness and reduced mobility of the valve may also be contributory. Since the sound of tricuspid closure is not delayed in the absence of tricuspid disease and occurs 0.05 to 0.07 second after the QRS onset, one would expect splitting of the first sound to be a characteristic of mitral stenosis. This is not apparent by auscultation because the intense sound of mitral closure obscures the faint preceding sound of tricuspid closure. Kelly[1] has stated that the sound of tricuspid closure contributes little to the first sound in mitral stenosis and Dock[2] has suggested that tricuspid closure is faint because of the frequent presence of associated pulmonary hypertension which causes the tricuspid leaflets to move together just before closure, thus reducing the intensity of the sound. However, Leatham[3] has published a phonocardiogram of a patient with mitral stenosis with a prominently split first sound and Wells[4] has cautioned against overlooking a prominent tricuspid component in making measurements of the Q-1st sound interval.

While it may be correct to use the term "first heart sound" to describe auscultatory findings in mitral stenosis, phonocardiographers should be more precise and should refer to the tricuspid and mitral components of the first sound as discrete and separate events when they can be identified. This is particularly important when studying the interval from the onset of the QRS complex to the sound of mitral closure in mitral stenosis and other conditions. It is the purpose of this study to demonstrate that the sound of tricuspid closure can be identified in the phonocardiograms of the majority of patients with mitral valve disease and that in many of these patients, it produces a significant, audible component of the first heart sound at the apex.

Phonocardiograms were recorded in 40 patients with surgically proven mitral valve disease. Twenty patients had tight mitral stenosis without mitral insufficiency and the majority were improved by valvulotomy. Twenty patients had combined mitral stenosis and mitral insufficiency with a fixed mitral valve orifice greater than 1.0 cm.^{2}, and a prominent regurgitant jet palpable in the left atrium at surgery. In 12 of these patients valvulotomy with or without an attempt to reduce the degree of mitral insufficiency was performed. No clinical improvement occurred. In 8 patients no valvulotomy was performed. Phonocardiograms were recorded in recumbency, at paper speeds of 75 mm. per second using a Sanborn Twin Beam oscillograph. Simultaneous electrocardiograms, apex impulses, and carotid pulses were recorded for timing purposes The peak of the largest deflection of the identified components of the first sound was used in all measurements. The peak was found to occur from 0.01 to 0.02 second after the onset of the sound.

The sound of tricuspid closure was identified in 17 of 20 patients with tight mitral stenosis and 18 of 20 patients with combined mitral stenosis and insufficiency. The sound is usually of low frequency, faint and is usually inaudible. It is most consistently recorded over the tricuspid area (lateral to the

From the Cardiovascular Research Laboratory, Stanford University School of Medicine, San Francisco, Calif.

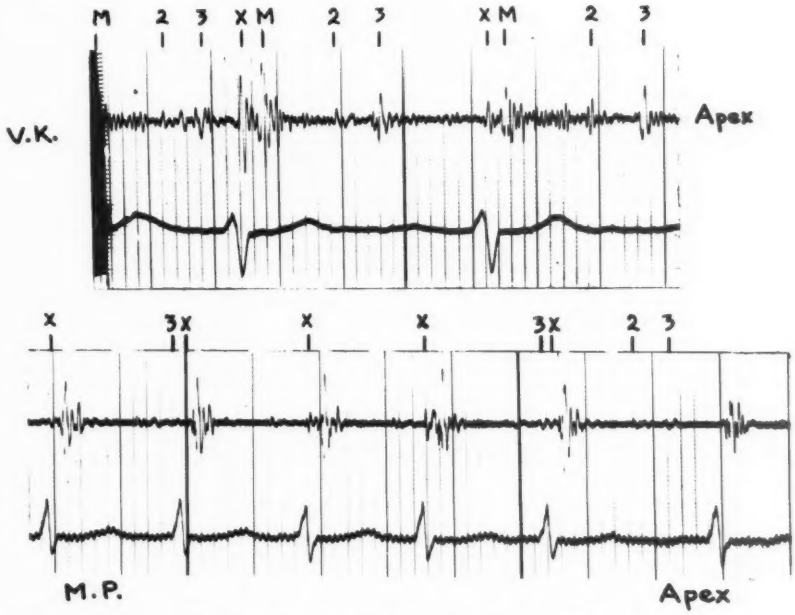

FIG. 1. Apex phonocardiograms from 2 patients with combined mitral stenosis and mitral insufficiency with a simultaneously recorded electrocardiogram (lead II). Note accentuation of the tricuspid component (x) of the first sound after short diastolic periods. In each record a third heart sound (3) is present. Note: In the upper tracing the first sound (M) and the QRS complex of the initial cardiac cycle are not visible but the T wave and the second sound can be seen.

left sternal margin in the fifth intercostal space) or between this area and the cardiac apex. It occurs from 0.05 to 0.07 second (mean 0.062 second) after the QRS onset. It occurs either simultaneously with or up to 0.02 second after the onset of precordial motion due to ventricular systole. When recorded with simultaneous tracings of right ventricular pressure, the tricuspid sound coincides with the onset of pressure rise in the right ventricle.[5]

An important characteristic of the tricuspid sound is its variation of intensity in relation to the length of the preceding diastole, when the ventricular rhythm is irregular due to atrial fibrillation. The leaflets of the tricuspid and mitral valves are thrust most widely apart during the rapid filling period in early diastole. If ventricular systole occurs during this period a louder sound will be produced than would occur if ventricular systole began later when the valve leaflets have floated back toward a position of partial closure. In patients with atrial fibrillation who do not have mitral valve disease, a graphic analysis of the intensity of the first heart sound and the length of diastole preceding the sound will reveal a predictable inverse relationship—the sound is loud following short diastoles and faint following long diastolic periods.[6] The sound of tricuspid closure should behave in a similar manner even in the presence of mitral valve disease, providing the tricuspid valve is normal. This feature was examined. Atrial fibrillation with sufficient variation in the duration of diastole to alter the intensity of the sound of tricuspid closure was present in 6 patients. After short diastolic periods the sound of tricuspid closure is invariably accentuated. In addition, the sound of mitral closure is further delayed because of the higher left atrial

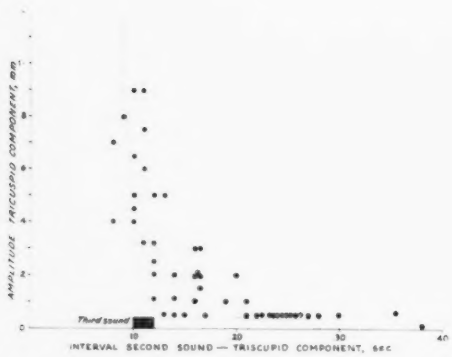

FIG. 2. Graphic relationship of the intensity of the tricuspid component of the first sound and the length of the preceding diastolic period in patient M.P. A portion of the phonocardiogram from which this analysis was made is illustrated in figure 1. The black rectangle marks the position of the third heart sound.

pressure.[4] Under these circumstances the sound of tricuspid closure may be identified as the initial component of a split first sound after short diastolic periods. Examination of the upper tracing in figure 1 demonstrates these features. In the first cycle there is accentuation of the sound of tricuspid (*x*) and and mitral (*M*) closure when compared to the second cycle. The interval from the second sound to the sound of mitral closure is 0.31 second for the first cycle and 0.54 second for the second cycle. The interval from the onset of the QRS complex to the onset of the sound of tricuspid closure is 0.05 second in each cycle, while the sound of mitral closure begins 0.12 second (first cycle) and 0.10 second (second cycle) after the QRS onset. The lower tracing in figure 1 also demonstrates that the sound of tricuspid closure is accentuated when ventricular systole begins at the time of rapid ventricular filling (third and fourth cycles), and the sound is faint or absent when ventricular systole begins after a long diastolic period (second, fifth, and sixth cycles). The relationship between the intensity of the sound of tricuspid valve closure and the length of the preceding diastolic period is graphically illustrated in figure 2. Despite variations in intensity of the sound of tricuspid closure no consistent variation is observed in the Q to tricuspid sound interval. Loud sounds of tricuspid closure after short diastoles do not appear to occur later than faint sounds. It is possible that more precise measurements of a larger number of records may reveal that the loud sounds occur slightly later than the faint sounds in a manner similar to the sound of mitral closure in the absence of mitral valve disease.

The predictable variation of the intensity of the sound of tricuspid closure in relation to the length of the preceding diastole removes any possibility that the sound is due to any mechanism other than A-V valve tension. In most records with irregular ventricular rhythm, it is possible to observe a gradual transition from the faint, low frequency sounds preceding mitral closure to the loud, audible, accentuated sounds after very short diastoles. In addition, the sound occurs at the time of the onset of right ventricular pressure rise and is loudest at the tricuspid area. The sound is not due to impact of the heart against the chest wall, since it has been recorded directly from the surface of the exposed heart.[5]

It appears likely that similar low frequency sounds recorded by other workers in the past are sounds of tricuspid valve closure. In two papers by Cossio[7, 8] vibrations of a sound preceding the sound of the mitral closure (labeled "o") can be seen to be of greater intensity after short diastoles, although the author did not comment upon this phenomenon. Figure 3 is a reproduction of one of Cossio's illustrations[7] which demonstrates a probable tricuspid sound (*o*) preceding the louder sound of mitral closure (*1*). A similar phenomenon appears in a paper by Groedel and Kisch,[9] who interpreted the sound as a presystolic murmur occurring in the presence of atrial fibrillation. Battro[10] suggested that the sound may be due to mitral reflux occurring during isometric contraction. This concept has been recently revived,[11] curiously enough in an era in which hemodynamic measurements have shown that in mitral stenosis mitral closure does not occur until the left

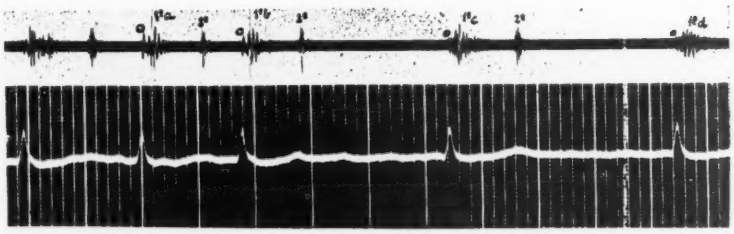

FIG. 3. Apex phonocardiogram with simultaneous electrocardiogram from a patient with mitral stenosis from Cossio and Berconsky.[7] Note how sound (*o*) preceding the sound of mitral closure *(1)* is accentuated following short diastolic periods (second and third cycles). *(Reproduced by permission from Rev. argent. cardiol.* **10**: *162, 1943.)*

ventricular pressure exceeds the left atrial pressure, which makes the concept of mitral reflux occurring before this event untenable.

Faint, low frequency sounds preceding the loudest component of the first sound at the apex have been previously ascribed[12,13] to sounds of muscular contraction. It is apparent from this study that similar sounds can be produced by tricuspid valve closure in mitral valve disease and it is quite possible that all such sounds ascribed to muscular contraction are due to A-V valve closure.

It is quite apparent from the magnitude of the tricuspid sound after short diastoles in atrial fibrillation that Q to first sound measurements made to the onset of the first sound could be erroneously short since the measurement would actually be a Q to tricuspid sound interval (fig. 1). It is possible that the short Q to first sound intervals recently reported by Proctor[15] were due to such an error in measurement.

The presence of the sound of tricuspid closure in both tight mitral stenosis and mitral stenosis with significant insufficiency indicates that its identification offers no diagnostic information except that there is a delay of mitral closure.

SUMMARY

The sound of tricuspid valve closure has been identified in 35 of 40 phonocardiograms of patients with mitral valve disease. Identification of the sound is facilitated by the delay of closure of the mitral valve thus separating these 2 components of the first heart sound. When the ventricular rhythm is irregular due to atrial fibrillation, the intensity of the sound is inversely proportional to the length of the preceding diastolic interval. When the sound of tricuspid closure is accentuated, it may be identified by auscultation as the initial component of a split first sound mesial to the apex. Measurement of the interval from the onset of the QRS complex of the electrocardiogram to the "first heart sound" should be made to the mitral component of the first sound when this can be identified on the phonocardiogram.

SUMMARIO IN INTERLINGUA

Le sono del clausion del valvula tricuspidal esseva identificate in 35 ex 40 phonocardiogrammas de patientes con morbo del valvula mitral. Le identification del sono es facite plus facile per le retardo del clausion del valvula mitral, con le resultato de un separation del 2 componentes del prime sono cardiac. Quando le rhythmo ventricular es irregular in consequentia de fibrillation atrial, le intensitate del sono es inversemente proportional al longor del precedente intervallo diastolic. Quando le sono del clausion tricuspidal es accentuate, illo pote esser identificate per auscultation como le componente initial de un findite prime sono, medial con respecto al apice. Le mesuration del intervallo ab le declaration del complexo QRS del electrocardiogramma usque al "prime sono cardiac" deberea terminar se al componente mitral del prime sono si iste componente pote esser identificate in le phonocardiogramma.

REFERENCES

1. Kelly, J., Jr.: Diagnostic value of phonocardiography in mitral stenosis. Mode of production of first heart sound. Am. J. Med. **19**: 862, 1955.
2. Dock, W.: Heart Sounds, Cardiac Pulsations and Coronary Disease. Lawrence, University of Kansas Press, 1956.
3. Leatham, A.: Splitting of the first and second heart sounds. Lancet **2**: 607, 1954.
4. Wells, B.: The assessment of mitral stenosis by phonocardiography. Brit. Heart J. **16**: 261, 1954.
5. Leo, T., and Hultgren, J.: Phonocardiographic characteristics of tight mitral stenosis. To be published.
6. Rytand, D.: The variable loudness of the first heart sound in auricular fibrillation. Am. Heart J. **37**: 187, 1949.
7. Cossio, P., and Berconsky, I.: El primer ruido cardiaco y el soplo presistolico en la etrechez mitral con fibrilacion auricular. Rev. Argent. de Cardiol. **10**: 162, 1943.
8. Cossio, P.: Primer ruido cardiaco. Arch. del Inst. de Cardiol. de Mexico **15**: 201, 1945.
9. Grodel, F., and Kisch, B.: Presystolic murmur without auricular systole. Exper. Med. & Surg. **2**: 319, 1944.
10. Battro, A., Braun-Menéndez, E.: Estudio fonocardiografico de la estrechez mitral. Rev. Argent. de Cardiol. 4-1, 1937.
11. Nichols, H., Likoff, W., Goldberg, I., and Fuchs, M.: The genesis of the "presystolic" murmur in mitral stenosis. Am. Heart J. **52**: 379, 1956.
12. Rappaport, M., and Sprague, H.: The graphic registration of the normal heart sounds. Am. Heart J. **23**: 591, 1942.
13. Orias, O., and Braun-Menéndez, E.: The Heart Sounds in Normal and Pathological Conditions. London, New York, Toronto, Oxford University Press, 1939.
14. Counihan, R., Messer, A. L., Rappaport, M., and Sprague, H.: The initial vibrations of the first heart sound. Circulation **3**: 731, 1951.
15. Proctor, M., Walker, R., Hancock, E., and Abelmann, W.: Phonocardiogram in mitral valvular disease: Correlation with left heart catheterization and operative findings. Abstracted, Circulation **16**: 927, 1957.

Clinical Aspects of Gallop Rhythm with Particular Reference to Diastolic Gallops

By W. Proctor Harvey, M.D., and John Stapleton, M.D.

Gallop rhythm represents one of the most important but still very confused aspect of clinical auscultation of the heart. Most gallop rhythms are unrecognized or misinterpreted. This is unfortunate because a gallop, depending on the type, often represents the earliest clinical evidence of congestive heart failure. After analyzing the various classifications of gallops[1–21] we have used the following clinical classification which we consider physiologic, practical, and simple. Gallops are first divided into systolic and diastolic gallops (fig. 1).

The *systolic gallop* (or click) is an extra sound occurring in systole, generally best heard at the apex and usually representing a benign finding.[7, 8, 18] Its exact etiology is not known, but in a number of cases appears to be extracardiac in origin. A few of the patients with this benign systolic sound have a past history of severe pneumonia, pleurisy, or less commonly empyema. One could speculate in such cases as to the possibility of adhesions contributing to this sound. The majority, however, have a completely negative history. In addition to this benign type of systolic sound there may be systolic sounds heard in conjunction with organic heart disease. For example, in aortic insufficiency a systolic sound may be heard at the apex, base, and peripheral arteries which has been termed a systolic ejection sound, "pistol shot," systolic click, or gallop.[5, 6, 13, 14] When this is present (e.g., with aortic insufficiency) one usually has no difficulty in determining the presence of organic heart disease. In aortic insufficiency of a severe degree the first heart sound is often faint and the ejection sound is early, thereby at times causing confusion with the first heart sound. In addition, a systolic sound may likewise be heard over an enlarged pulmonary artery from any cause such as atrial septal defect, ventricular septal defect, pulmonic stenosis, primary pulmonary hypertension, idiopathic dilatation of the pulmonary artery, etc. We have found this sound commonly associated with enlargement of the pulmonary artery segment, and it is best heard over the pulmonic area or third left intercostal space rather than at the apex, as is the case with the benign systolic click or gallop. This sound occurring in systole has been termed an ejection sound, and as with the systolic sound produced with aortic insufficiency, it is probably produced by sudden filling of the pulmonary artery during ventricular systole. The finding of this systolic sound in association with organic heart disease does not of itself indicate a poor prognosis, but its presence may be a valuable auscultatory clue to the presence of a pulmonary artery enlarged from various causes, such as congenital heart disease.

Diastolic Gallops. After determining that the gallop occurs in diastole it must be further subdivided into 2 components, the atrial diastolic gallop and the ventricular (or third heart sound type) diastolic gallop (fig. 1). Further classification of the diastolic gallop in this manner is a necessity because the atrial gallop does not usually carry the same serious prognosis that is associated with the ventricular diastolic gallop.

Atrial Gallop. This gallop sound is related to atrial contraction and may occur in the absence of any evidence of cardiac decompensation. It is frequently heard when there is a delay in atrioventricular conduction and the P-R interval is prolonged (fig. 2 *top*). In

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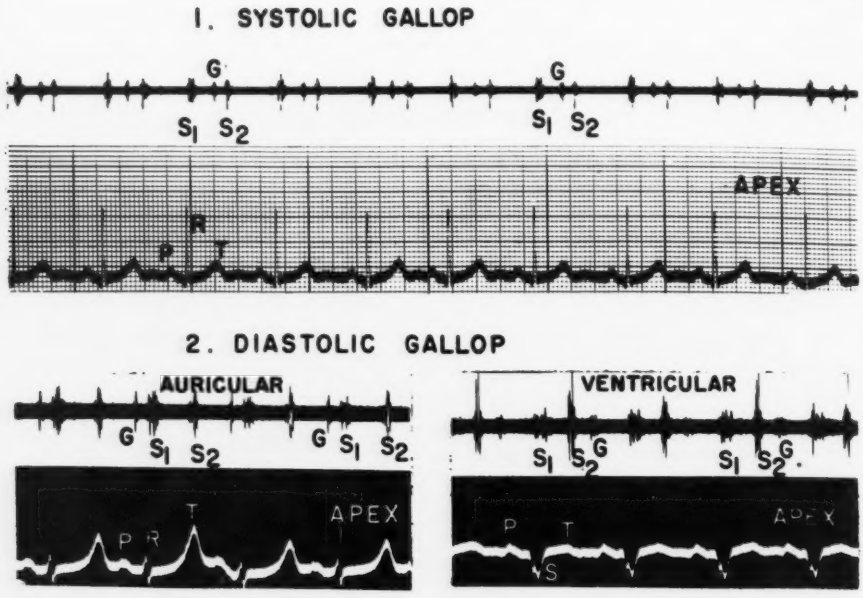

FIG. 1. *Upper Tracing.* Benign systolic gallop (or click) (*G*) in a 17-year-old girl with no heart disease. *Left Lower Tracing.* Atrial diastolic gallop (*G*) in patient with acute renal insufficiency. No failure. *Right Lower Tracing.* Ventricular diastolic gallop (*G*) in patient with arteriosclerotic heart disease, congestive failure, previous myocardial infarction.

such an instance one hears the atrial sound, the first heart sound (which is faint because of the prolonged P-R interval), and the second heart sound. Also, when the P-R interval is still within upper normal limits, an atrial gallop sound is sometimes heard (fig. 2 *middle*).

A patient has been observed who had an attack of acute rheumatic fever 20 years previously. No valvular deformity resulted, but a conduction defect in the form of first degree heart block persisted. An atrial diastolic gallop was often present, usually dependent on heart rate. It was usually best heard with a slight tachycardia in the range of 100. At no time had he ever shown any signs or symptoms of heart failure. His gallop, though diastolic, naturally has not represented one of poor prognosis. He had always been instructed to lead a normal life and not restrict his activities in any way.

Atrial gallop is frequently heard in hypertension (fig. 3) without prolongation of the P-R interval. This may be present before the onset of any heart failure, and in itself does not necessarily denote serious heart disease. Once failure ensues, however, the atrial gallop may persist, but now there appears the ventricular gallop (of third heart sound type), the gallop of heart failure (fig. 3 *top*). Why the atrial sound is accentuated with hypertension is unclear. Infrequently we have heard an atrial sound sometimes simulating a gallop rhythm in a perfectly normal heart.

Ventricular (Third Heart Sound) Gallop. This is the gallop which appears to be almost always associated with heart failure (figs. 3-6). It often occurs as the first sign that one can detect clinically of serious heart disease and cardiac decompensation. This gallop sound appears in the earlier part of diastole, later in timing than an opening snap, but at the same time as the physiologic third heart sound in children and youths (the basis for the term "third heart sound gallop"). The normal physiologic third sound, a common

findi - in children and young adults, becomes less equent in the years 20 to 30, after 30 still ss common, and after 40 rare as a benign nding. As a rule, a sound with this timi in a person in his forties, fifties, and over epresents a ventricular diastolic gallop. The ventricular gallop is the most important as well as the most common type of gallo The exact cause of this sound is a matt of debate at the present time, although we f l that it is probably related to movement of the A-V valves. The ventricular diastolic allop is found commonly, if one searches for it in the presence of congestive heart failure. It is more rare in patients with mitral stenosis, where, instead, the opening snap is heard. In fact, the presence of a ventricular diastolic gallop makes most unlikely the diagnosis of the uncomplicated "tight" mitral stenosis. The common denominator when a ventricular diastolic gallop is present, regardless of the etiology of heart disease, is congestive heart failure, and except in rare instances indicates a serious heart derangement.

Like all gallops, the ventricular diastolic is best heard in the apical region with the patient recumbent. At times it is better heard after slight effort when blood flow and heart rate are somewhat accelerated. However, a gallop sound occurring at a slow rate has the same significance as if it were heard at a fast rate. A gallop is a gallop, regardless of the ventricular rate. The majority of ventricular diastolic gallops are faint, being of low-frequency, and are therefore commonly overlooked. To hear it, one must listen specifically for this sound in early diastole, using the bell of the stethoscope with very light pressure, just making an air seal with the skin over the precordium. It the normal amount of pressure is applied, the extra sound may be greatly decreased or even become inaudible. The area where the gallop is best heard is generally along the lower left sternal border or apex, with the patient lying recumbent or turning to the left lateral position. Often listening while the patient is turning from flat to the left lateral position, or having the patient cough 5 or 6 times, may "bring out" this faint gallop sound. If the patient has any degree of emphysema or an increase in anterioposterior diameter of the chest, it should be kept in mind that auscultation over the xiphoid process or just under the ribs at the attachment of the diaphragm may be advantageous. With such a patient, having him sit up and lean forward may also serve to bring the faint sounds closer to the stethoscope. Using these technics, one can train himself to detect this faint gallop sound at lower heart rates. The same gallop with a sinus tachycardia (e.g., 110 to 120) is usually easily heard, whereas at a rate of 70 may be poorly heard unless one mentally "tunes in" on this low frequency sound and uses these technics.

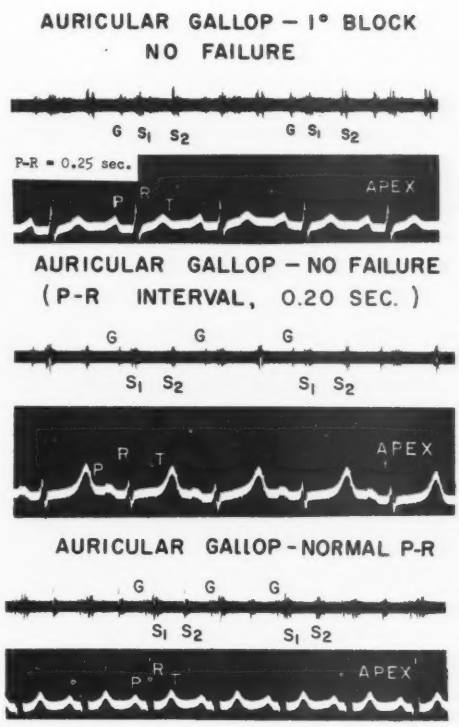

FIG. 2. Three patients with atrial gallop. *Upper Tracing.* Male, (52 years old) with anemia and first degree block (P-R 0.25 sec.). Note atrial gallop (G), faint first sound (S_1) and split second sound (S_2). *Middle and Lower Tracings.* Atrial gallop (G), with P-R intervals 0.20 second and 0.16 second respectively.

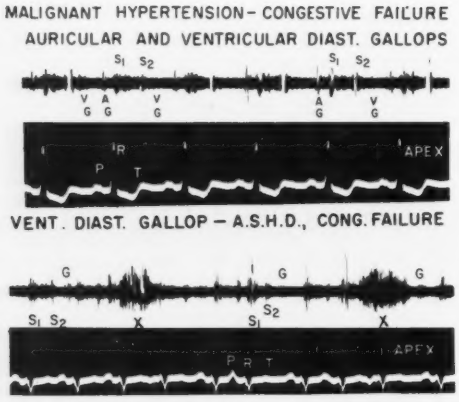

FIG. 3. *Upper Tracing.* Man with malignant hypertension and congestive failure. Blood pressure 280/160. Died 3 months later. Note atrial gallop (*A.G.*) preceding first sound (S_1) and ventricular gallop (*V.G.*) after second sound (S_2). *Lower Tracing.* Ventricular diastolic gallop (*G*) in male with arteriosclerotic heart disease and advanced congestive failure. Breath sounds (*X*) related to patient's dyspnea. Died several weeks later.

The importance of paying attention to this sound was first emphasized to us a number of years ago when we had the opportunity of following a large number of patients in the older age groups, before, during, and after various surgical procedures. We quickly learned that on examining patients prior to surgery, those having a ventricular diastolic gallop, even in the absence of other signs of cardiac decomposition, represented a "key group" which were prone to develop pulmonary edema or evidence of cardiac decompensation during or after the surgical procedure. By preparing preoperatively with digitalization, salt restriction, and mercurial diuretics, they were usually able to withstand their operation without any difficulty.

Prognosis of Ventricular Diastolic Gallops. There is no clear cut evidence to date as to the life expectancy once a gallop of this type is detected. In the past prognosis usually has been related to a gallop occurring in diastole, without specifying whether it is atrial or ventricular. As has been previously emphasized, the prognosis depends on the type of gallop present. It is obvious that a systolic click (or systolic gallop) and the atrial diastolic gallop in the absence of failure, do not carry the grave prognosis of ventricular diastolic gallop. We are at present in the process of studying the life expectancy of a large number of patients observed over the past 8 years where this type of classification has been used and the faint type of diastolic gallop has been carefully searched for. Although our figures are not completed at the present time, it appears that the prognosis after finding such a gallop will be approximately 3 to 5 years.

There are some points worthy of discussion concerning prognosis of ventricular diastolic gallops. The louder the gallop the poorer the prognosis. In general, this statement appears to correlate well with a decrease in life expectancy, particularly if there is a persistence of the gallop rhythm despite adequate medical treatment. For example, it is relatively common to hear a ventricular diastolic gallop following an acute myocardial infarction during the early acute stages. In the usual case, with the passage of time (several days to several weeks) the gallop sound may disappear. However, when it is particularly loud and persists after the acute episode, it generally is associated with permanent heart damage and chronic failure, and thus represents the poorer prognosis. The patient may have an acute myocardial infarction and a ventricular diastolic gallop coincident with the attack, and subsequently be left with no evidence of gallop or any other signs of heart failure. Naturally this represents a temporary sign of failure, with recovery, and indicates good myocardial reserve. The prognosis in this individual would then be related to other aspects of his underlying disease rather than to congestive heart failure. It appears also that persistent gallops well heard and associated with slight sinus tachycardia have more evidence of permanent serious heart failure, elevation of heart rate being an additional sign of a compensatory mechanism for cardiac decompensation. The patient may have a gallop rhythm of this type and concommitant extrasystoles. Following the extrasystoles for a few beats there is often a ac-

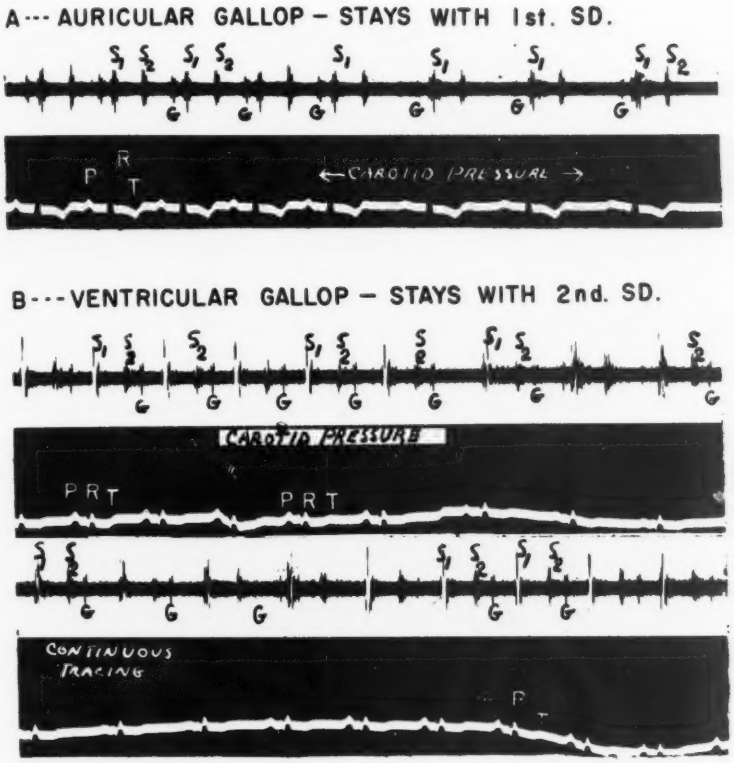

FIG. 4. *Upper Tracing.* 45-year-old male with first degree block, acute nephritis. Note atrial gallop (*G*) remains in presystole on slowing. *Lower Tracing.* 33-year-old man with chronic congestive failure with arteriosclerotic heart disease. Ventricular gallop (*G*) remains in early diastole. Note gallop sound in both tracings becomes faint for a few beats coincident with slowing.

centuation of the intensity of the gallop sound. This is known as the postextrasystolic accentuation of a gallop. On the other hand, an occasional patient without any evidence of heart disease, but having numerous extrasystoles, may have a few beats following the extrasystoles that have a third sound at the timing of a gallop. These are of no prognostic significance. In addition, coincident with and sometimes persisting for a while after tachycardias such as atrial tachycardia, a gallop rhythm may be heard which disappears shortly after termination of the attack. This also is usually benign. The faint ventricular diastolic gallop which has a better prognosis is not detected as an early sign of failure which disappears after routine measures for control of congestive failure. As a rule, treatment should be continued, which should result in prolongation of life in these patients.

Timing of Atrial and Ventricular Diastolic Gallops. When the heart rate is slow or normal, this is not difficult. The atrial diastolic gallop follows the atrial contraction in presystole, and therefore usually just precedes the first sound. The ventricular diastolic gallop (or third heart sound type) occurs at the timing of the physiologic third heart sound in early diastole, and is easily identified in the presence of a normal ventricular rate. However, when the rate becomes rapid, differentiation of the atrial from the ventricular type

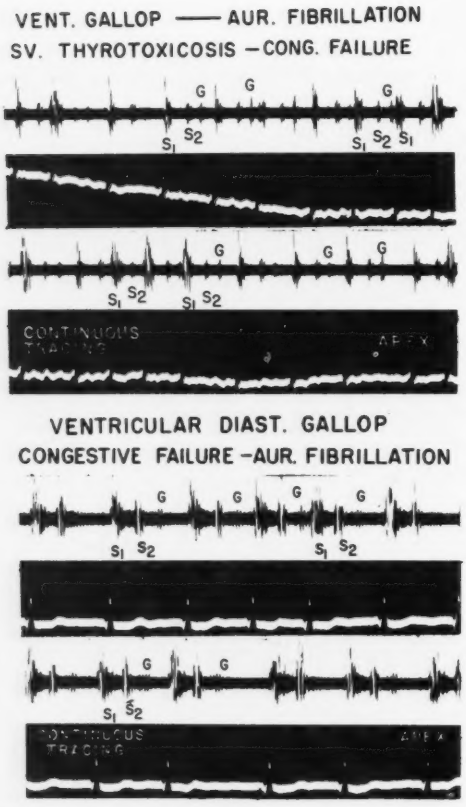

FIG. 5. Two patients with ventricular diastolic gallop (*G*) in presence of congestive failure and atrial fibrillation. Depending on length of diastole the same gallop might be called by different observers, protodiastolic, mesodiastolic, or presystolic.

may be quite difficult, if not impossible, unless slowing occurs. We have found carotid sinus pressure of great value for this differentiation (fig. 4). When the heart rate is slowed, the atrial gallop will be heard in relation to the first sound in presystole during the slower intervals. On the other hand, a ventricular diastolic gallop sound will remain in conjunction with the second heart sound, occurring shortly after it. When carotid sinus pressure causes a slowing of the heart rate, there may be a temporary period of several beats where no gallop sound is detected, but with the gradual resumption of heart rate, the extra sound can be identified without difficulty in its proper place. Sometimes the gallop sound does not disappear with the slowing, even for a few beats. The technique of listening to the heart at the same time carotid sinus pressure is applied is recommended. When doing so, the stethoscope can be placed on the chest wall and left there, or can be held by another observer. Pressure is applied usually on the right side at the angle of the jaw, making sure a carotid arterial pulsation is felt. Pressure should be firmly applied but only for a duration of several seconds, releasing for 4 to 5 seconds, and then re-applying intermittently. Once slowing is heard, the pressure is stopped and one can pay strict attention to the auscultatory events.

To show the importance and necessity of differentiating the atrial from the ventricular type of diastolic gallop, the following case is cited. A 44-year-old woman was seen for evaluation of a sound occurring in diastole. Her past history was of importance in that as a young girl her bedroom was next to that of her grandmother's who had heart disease and subsequently died from it. Apparently her grandmother had a prolonged course, characterized by chronic congestive heart failure, and this made a lasting imprint on this young girl. Four to 5 years later because of an episode, the details of which were not too clear, a diagnosis of embolus from the heart going to one of her arms was made. No residual resulted from this, but from that time on she was sure that she had heart disease and a cardiac neurosis was firmly entrenched. Although no specific etiology of heart disease had been established, she was seen by a number of physicians concerning her heart and approximately 20 years later, at the time of her examination, she was relatively incapacitated because of fatigue, periods of palpitation, weakness, and sighing respiration. Physical examination was not remarkable except for a diastolic gallop rhythm. By the old criteria and classification, the finding of a diastolic rhythm would mean a poor prognosis. When first examined her heart rate was elevated because of a sinus tachycardia, and the differentiation between an atrial and a ventricular diastolic gallop was not possible. However, with carotid sinus pressure a slowing of her ventricular rate occurred and it was evident that the gallop sound was atrial in type. This finding immediately removed the serious prognosis associated with a diastolic gallop. The next problem was an explanation of the atrial gallop. She had no hypertension, but there was a prolongation of her P-R interval to 0.23 seconds.

On reviewing her history, she was taking quinidine which had been given in an effort to control her sinus tachycardia. On the possibility that the P-R interval could be related to the quinidine, this was discontinued. Following this, the P-R interval shortened to upper normal limits with the disappearance of the gallop rhythm. This case illustrates that the mere labeling of a diastolic gallop in such a woman with a fixed cardiac neurosis, could only have served to add fuel to the fire. She was reassured that no heart disease was present. Unfortunately, her cardiac neurosis was so firmly established by this time that she will probably always have symptoms referable to her heart.

A ventricular diastolic gallop may indicate an unsuspected myocarditis, such as that of lupus erythematosus, or alert one's suspicion, in a patient with atypical chest pain, that myocardial damage is present despite a negative electrocardiogram at that particular time.

A ventricular diastolic gallop is almost always associated with slight pulsus alternans. Vice versa, the finding of a significant degree of pulsus alternans is almost always associated with a ventricular diastolic gallop. Both of these findings mean a failing heart, and too little attention has been paid to them in the past. In a similar fashion, alternation of heart sounds or alternation of heart murmurs is likewise frequently associated with a diastolic gallop rhythm and pulsus alternans, and all are generally associated with some degree of heart failure. In fact, gallops are often palpated, and in some patients a gallop may be even more easily felt than heard. As a rule, however, using the technics previously described to "bring out" a faint ventricular diastolic gallop, this will be heard if palpated.

A former clinical impression has been that gallops disappear with atrial fibrillation. This is certainly true of the atrial type diastolic gallop, since with the onset of fibrillation there is no contraction of the atria to produce the atrial gallop sound. On the other hand, the ventricular diastolic gallop does not disappear with atrial fibrillation (fig. 5). Because of the irregular heart rate it is more difficult to detect. A triple rhythm occurring with a regular rate is readily identified, whereas with an irregular rate, more concentration and longer auscultation are necessary. However, by listening specifically in the early portion of diastole, it will be heard, if present. The intensity of the gallop varies considerably with atrial fibrillation. After some beats it is inaudible or very faint, whereas after others it is well heard. This likewise adds to the difficulty in hearing the gallop with auricular fibrillation.

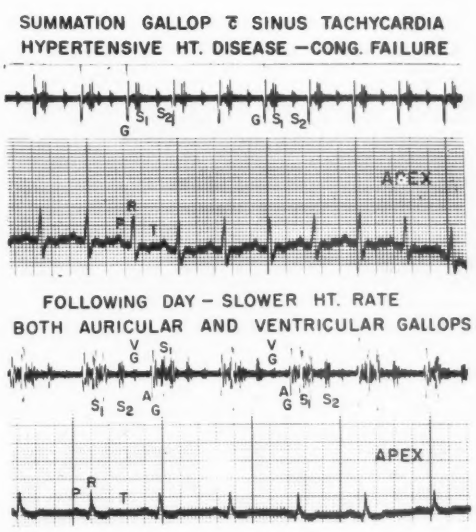

FIG. 6. Male, 47 years old with loud summation gallop (*G*) upper tracing. Blood pressure 210/110. Both atrial (*AG*) and ventricular (*V.G.*) gallops causing single summation gallop now heard separately with slower rate (*lower tracing*).

The fainter types of ventricular diastolic gallop tend to vary some with normal respiration. Sometimes a gallop sound is evident only on every third to fourth beat, again making it more difficult to detect.

Combination of Gallops. Occasionally one hears an extra loud gallop sound in diastole, or one may hear 2 sounds in diastole giving not a triple rhythm, but a quadruple rhythm (figs. 3 (*top*) and 6 (*bottom*). As already discussed, an atrial gallop may be heard for a number of years in a patient with hypertension but without signs or symptoms of heart failure. Once failure ensues, the ventricular gallop becomes evident, thus making 2 gallop sounds in addition to the 2 normal heart

sounds (fig. 3). Or, an individual having an acute coronary occlusion plus first degree heart block may likewise present 2 gallops, an atrial sound related to the prolonged P-R interval and a ventricular diastolic gallop associated with myocardial failure. The 2 normal sounds plus 2 gallop sounds result in 4 sounds, and this type of combination has been given descriptive terms at times, such as "cogwheel" or "locomotive" type.

Summation Gallop. In addition, it is possible to have both atrial and ventricular diastolic gallops occurring simultaneously. This often results in a very loud diastolic gallop, sometimes even louder than either of the 2 heart sounds. When analyzed on the phonocardiogram, it may be seen that these sounds coincide exactly. This is designated as summation gallop. When present, it may be possible when the heart rate slows (normally, or with carotid sinus pressure) to separate the atrial from the ventricular gallop, neither of which is as loud as the summation gallop made by both of them (fig. 6). It is also possible to have a systolic gallop in combination with a diastolic gallop or gallops. This is uncommon.

ACKNOWLEDGMENT

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REFERENCES

1. EVANS, W.: Heart murmurs: II. Brit. Heart J. **9**: 225, 1947.
2. FISHBERG, A. M.: Heart Failure. Philadelphia, Lea & Febiger, 1940.
3. FRIEDBERG, C. K.: Diseases of the Heart. Philadelphia, Saunders Co., 1957.
4. GOLDBERGER, E.: Heart Disease, Diagnosis and Treatment. Ed. 2. Philadelphia, Lea & Febiger, 1955.
5. LEATHAM, A., AND VOGELPOEL, L.: The early systolic sound in dilatation of the pulmonary artery. Brit. Heart J. **16**: 21, 1954.
6. —: Splitting of the first and second heart sounds. Lancet, **2**: 607, 1954.
7. LEVINE, S. A.: Clinical Heart Disease. Ed. 4. Philadelphia, Saunders Co., 1958.
8. —, AND HARVEY, W. P.: Clinical Auscultation of the Heart. Philadelphia, W. B. Saunders Company, 1949.
9. LEWIS, J. K., AND DOCK, W.: The origin of heart sounds and their variations in myocardial disease. J.A.M.A. **110**: 271, 1938.
10. LIAN, C.: The use of phonocardiography in clinical cardiology. Brit. Heart J. **10**: 92, 1948.
11. LUISADA, A. A.: The Heart Beat. New York, Hoeber, Inc., 1953.
12. MASSEY, F. C.: Clinical Cardiology. Baltimore, Williams & Wilkins Co., 1953.
13. MCKUSICK, V. A., HUMPHRIES, J. O'N., AND REID, J. A.: On cardiovascular sound. Further observations by means of spectral phonocardiography. Circulation **11**: 849, 1955.
14. —, MASSINGALE, O. N., JR., WIGOD, M., AND WEBB, G. N.: Spectral phonocardiographic studies in congenital heart disease. Brit. Heart J. **18**: 403, 1956.
15. ORIAS, O., AND BRAUN-MENÉNDEZ, E.: The Heart Sounds in Normal and Pathological Conditions. New York, Oxford Univ. Press, 1939.
16. SMITH, J. R.: Observations on the mechanism of the physiological third heart sound. Am. Heart J. **28**: 661, 1944.
17. READ, J., AND PORTER, W.: The efficacy of carotid sinus pressure in the differential diagnosis of triple rhythms. Am. J. Med. **19**: 177, 1955.
18. THOMSON, W. P., AND LEVINE, S. A.: Systolic gallop rhythm: Clinical study. New England J. Med. **21**: 1021, 1935.
19. WEITZMAN, D.: The mechanism and significance of the auricular sound. Brit. Heart J. **17**: 70, 1954.
20. WHITE, P. D.: Heart Disease. Ed. 4. New York, The Macmillan Company, 1951.
21. WOOD, P.: Diseases of the Heart and Circulation. Ed. 2. Philadelphia, J. B. Lippincott Company, 1956.

The Austin Flint Murmur: Its Differentiation from the Murmur of Rheumatic Mitral Stenosis

By Jack P. Segal, M.D., W. Proctor Harvey, M.D., and Michael A. Corrado, M.D.

After clinical evaluation of patients with severe aortic insufficiency, it has become evident that differentiation of the Austin Flint murmur from that of mitral stenosis is possible in the majority of cases.[1-5] If carefully searched for, all of our patients with severe aortic insufficiency have an apical diastolic rumble (so-called Austin Flint murmur). By utilization of the clinical features derived from a careful history, physical examination, x-rays, and electrocardiography, it is possible in the majority of cases to determine whether the apical diastolic rumble represents an Austin Flint murmur or the murmur of organic mitral stenosis. For all practical purposes this problem in differential diagnosis only exists in those patients in whom the rheumatic etiology is the basis for their aortic insufficiency. Since surgical correction of both mitral stenosis and aortic insufficiency can now be attempted, it becomes extremely important to determine which patients with aortic insufficiency have associated mitral stenosis.

These observations are based on a careful clinical evaluation of over 400 patients with severe aortic insufficiency. The average age was about 35. Males outnumbered females in a ratio of 3 to 1. The etiology of aortic insufficiency in our series was rheumatic in over 80 per cent. The remaining cases were divided between the syphilitic, congenital and traumatic etiologies. Occasionally, aortic insufficiency was associated with a dissecting aortic aneurysm, or with the Marfan syndrome.

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In every case a careful clinical evaluation consisting of a history and physical examination, electrocardiogram and chest film was performed. Additional studies such as phonocardiograms and right and left heart catheterization were sometimes performed.

To establish the diagnosis of aortic insufficiency, the following 2 criteria were essential: (1) a decrescendo, blowing aortic diastolic murmur (usually at least grade IV), and (2) a diastolic blood pressure of 40 mm. Hg or below. In almost all cases the diastolic sounds were heard down to zero. In all patients, peripheral signs of aortic insufficiency, such as the waterhammer pulse, pistol shot sound, and Duroziez's sign, were present. In all but one of the rheumatic cases the presence or absence of mitral stenosis was confirmed either at autopsy or by surgical exploration, and in some cases by both. In those cases diagnosed as syphilitic aortic insufficiency, there was no history of rheumatic fever, often the history of a primary syphilitic lesion, often a positive serology, and frequently calcification of the ascending aorta.

In table 1 are listed those clinical features important in differentiating those patients with aortic insufficiency alone from those with both aortic insufficiency and mitral stenosis combined.

The following special comments are in order:

The opening snap of the mitral valve is heard only in those patients with associated mitral stenosis. Of interest, is the fact that in patients with combined aortic insufficiency and mitral stenosis, the opening snap appears to be delayed; instead of occurring at the usual interval of .06 to .08 second after the second sound, it occurs from 0.11 to 0.12 second later.

TABLE 1.—*Comparison of Clinical Features in Differentiating the Austin Flint Murmur and Rheumatic Mitral Stenosis*

	Aortic insufficiency with Austin Flint murmur	Aortic insufficiency with associated mitral stenosis
Sex	More frequent in males	More frequent in females
Hemoptysis	Almost never	Strong evidence for M. S.
Rhythm	Almost always normal sinus	Atrial fibrillation frequent
M_1	Usually faint	Usually loud
P_2	Normal or increased	Usually loud
Ventricular gallop (early diastolic)	Always present	Absent with significant M.S.
Opening snap	Absent	Present but usually delayed
Apical diastolic murmur	Usually early and mid-diastolic	Often presystolic accentuation
X-ray	1- Boot shaped heart 2- Generalized, slight esophageal displacement	1- Straightening of left border 2- Localized, distinct esophageal displacement
E. K. G.	1- Sinus rhythm 2- Often PR interval prolonged 3- Left ventricular hypertrophy	1- Often atrial fibrillation 2- Broad notched P waves 3- Vertical axis

In patients with severe aortic insufficiency 3 murmurs are almost always *heard at the apex*: a systolic murmur of mitral insufficiency, a very early diastolic blowing murmur transmitted from the aortic area, and the Austin Flint murmur which is usually accentuated in mid-diastole. In addition, a ventricular diastolic gallop (early diastolic gallop) is almost always heard. Very frequently a loud early systolic ejection sound of aortic origin is well heard at the apex. In fact, this sound is often mistaken for an accentuated first sound.

With aortic insufficiency alone, the apical diastolic murmur (Austin Flint murmur) is best heard in early and mid-diastole, and usually starts coincident with or immediately after the ventricular gallop. This murmur is usually of grade III intensity, but in some cases has been as loud as grade VI, and sometimes is associated with an apical diastolic thrill. Usually presystolic accentuation is not present, but with more rapid heart rates, particularly with a short P-R interval presystolic accentuation may occur. With associated mitral stenosis the diastolic rumble is "longer," extending throughout diastole and usually associated with presystolic accentuation if sinus rhythm is present.

To summarize: the patient with an Austin Flint murmur (pure aortic insufficiency as the only lesion) is most likely male, with moderate or slight progressive dyspnea and/or angina pectoris, and normal sinus rhythm. The second sound over the pulmonic area is normal or slightly accentuated, and the first sound at the apex is often faint. A systolic ejection sound is a common finding over the base of the heart and, frequently, also over the entire precordium. At the apex a systolic murmur, ventricular diastolic gallop, early diastolic blowing murmur transmitted from the aortic area, and an apical diastolic rumble usually accentuated in mid-diastole, are heard. The electrocardiogram shows normal sinus rhythm, left ventricular hypertrophy, and frequently a prolonged P-R interval. X-ray and fluoroscopy reveal moderate enlargement of the left ventricle, no enlargement of the pulmonary artery segment, and no or very slight posterior displacement of the esophagus.

In contrast, the patient with associated organic mitral stenosis would more likely be a female with a history of moderate to marked exertional dyspnea, frequently paroxysmal, and often associated with cough and hemoptysis. The rhythm may be normal sinus, but atrial fibrillation or flutter is not an unusual occurrence. On auscultation the second sound over the pulmonic area and the apical first sound are accentuated, and an opening snap of the mitral valve is present. The apical diastolic rumble is frequently accentuated in presystole. X-ray and fluoroscopic examination reveal straightening of the left hea

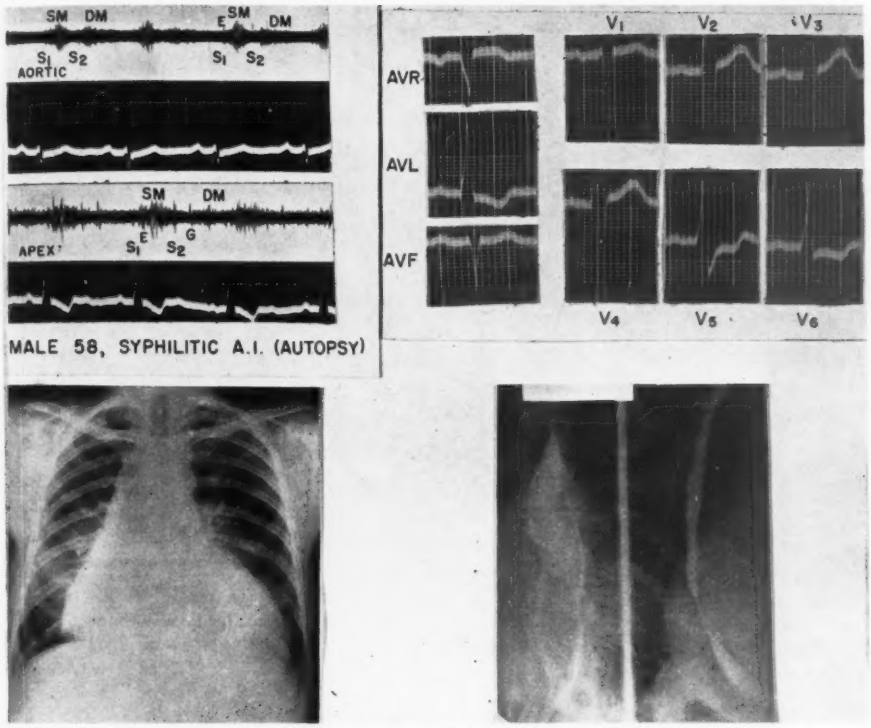

FIG. 1. Male, 58, with syphilitic aortic insufficiency (autopsy). Phonocardiogram (*upper left*), aortic area; note ejection sound (*E*), diamond-shaped early systolic murmur (*SM*), and decrescendo diastolic murmur (*DM*); at apex, note faint first sound (S_1), ejection sound (*E*), systolic murmur (*SM*), second sound (S_2), gallop (*G*) and Austin Flint rumble (*DM*). Chest x-ray shows classic left ventricular enlargement and esophagus slightly displaced posteriorly. Electrocardiogram shows left ventricular hypertrophy.

border, possibly right ventricular enlargement, and localized posterior displacement of the esophagus due to an enlarged left atrium. Calcification of the mitral valve might be present. The electrocardiogram generally shows normal or right axis deviation, possible right ventricular hypertrophy, broad-notched P-waves, and sometimes atrial fibrillation or flutter.

Aortic Insufficiency Alone. The following two cases represent classical instances of free aortic insufficiency associated with Austin Flint murmur.

Patient J.M. (fig. 1). A 58-year-old white male with syphilitic aortic insufficiency. At approximately age 20 he had syphilis. He was asymptomatic until 18 months prior to admission when the onset of dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and ankle edema occurred. There was no history of angina pectoris. On physical examination he was thin and appeared chronically ill. Pulse was 92, regular. Blood pressure 130/30-0. No neck vein distention. Lungs were clear to percussion and auscultation. The heart was enlarged to the anterior axillary line in the sixth left intercostal space, and enlarged 1½ inches to the right of the sternal border in the second right intercostal space. Visible systolic pulsations were seen over the aortic area where a systolic and diastolic thrill were palpable. The second sound was not accentuated over the aortic area, but the pulmonic second sound was increased in intensity. At the aortic area a grade V short systolic murmur, and a grade VI diastolic murmur were present. At the apex a grade III systolic murmur and a grade II+ apical diastolic murmur without presystolic accentuation were heard. A definite ventricular diastolic gallop was noted. The elec-

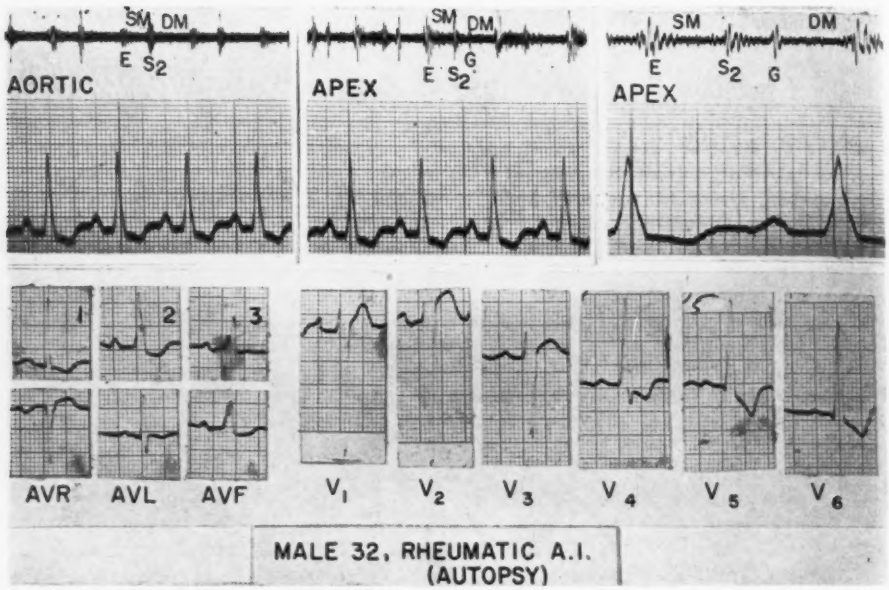

FIG. 2. A 32-year-old male with rheumatic aortic insufficiency (autopsy). Phonocardiogram, aortic area; ejection sound (*E*), systolic murmur (*SM*), and diastolic murmur (*DM*). Apex; loud ejection sound (*E*) and ventricular diastolic gallop (*G*). Note the systolic murmur (*SM*) and Austin Flint murmur (*DM*). Electrocardiogram shows left ventricular hypertrophy and strain.

trocardiogram revealed left ventricular hypertrophy. Fluoroscopic examination revealed transverse enlargement of the heart, both to the right and left, with definite left ventricular enlargement. The aortic pulsations were greatly increased. There was moderate generalized posterior displacement of the esophagus on barium swallow, and moderate systolic expansion of the left atrium was seen. The clinical impression was syphilitic heart disease with aortic insufficiency, Austin Flint murmur, relative mitral insufficiency. A plastic aortic valve was inserted and the patient expired shortly after leaving the operating room. Post mortem examination confirmed the clinical diagnosis of syphilitic aortic insufficiency. The aortic valve admitted 2 fingers. A syphilitic aneurysm of the ascending aorta was also present. The mitral valve was normal.

Summary. A patient with classical syphilitic heart disease and free aortic insufficiency. At the aortic area a loud diamond-shaped aortic systolic murmur associated with a palpable thrill was present, but at autopsy no evidence of aortic stenosis was found. In contrast to the murmur of aortic stenosis, this aortic systolic murmur was short and reached its peak relatively early in systole. In all of our patients having the severe form of aortic insufficiency an associated aortic systolic murmur has been present. This murmur differs from that of aortic stenosis by being shorter in duration and occurring earlier in systole. With significant aortic stenosis the systolic murmur extends almost to aortic valve closure, and the peak of this diamond-shaped murmur occurs later in systole. On auscultation at the apex, the first heart sound was described by one observer as being accentuated. However, as shown on the phonocardiogram, an early systolic ejection sound was being mistaken for the first heart sound, which was actually faint. The phonocardiogram also confirmed the apical systolic murmur, ventricular diastolic gallop, and mid-diastolic murmur (Austin Flint). The classical x-ray and electrocardiographic findings already described were present.

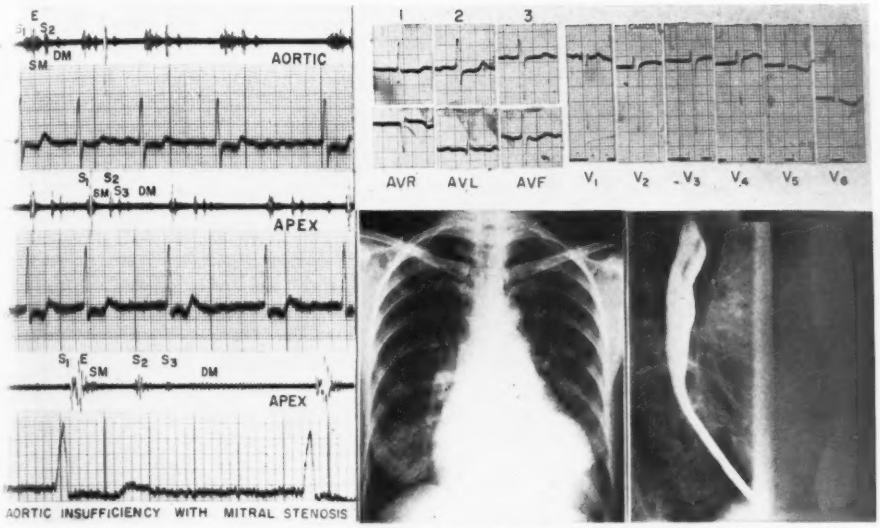

FIG. 3. A 52-year-old female with slight aortic insufficiency and tight mitral stenosis (surgical exploration). Phonocardiogram, aortic area; prominent ejection sound (*E*) and blowing diastolic murmur (*DM*). Apex; loud first sound (S_1), short systolic murmur (*SM*), opening snap (S_3),* and diastolic rumble (*DM*). X-ray shows left ventricular enlargement, straightening of the left heart border, and posterior displacement and compression of the esophagus. Electrocardiogram, left ventricular hypertrophy and strain (½ standardized).

Patient J.M. (fig. 2). A 32-year-old man with rheumatic heart disease. Increasing fatigue, dyspnea on exertion, and paroxysmal nocturnal dyspnea had been present for a year and a half, and orthopnea for 4 months. He had been treated for subacute bacterial endocarditis at the age of 23 and again at the age of 30. Physical examination: Blood pressure 160/40-0. Lungs were clear to percussion and auscultation. The heart was enlarged to the anterior axillary line. Rate 92 and regular with frequent premature ventricular contractions. At the aortic area were heard a grade III short aortic systolic murmur and a grade IV diastolic blowing murmur, loudest at the left sternal border. At the apex a grade II apical systolic, a grade III Austin Flint rumble, and a ventricular diastolic gallop were present. The liver was palpated one fingerbreadth below the right costal margin, and the spleen was not felt. One-plus pretibial edema was present. The chest x-ray revealed the heart markedly enlarged to the left with some enlargement of the left atrium as noted on barium swallow. Electrocardiogram revealed frequent premature ventricular contractions with periods of bigeminy. The P-R interval was 0.22 second. The interpretation was left ventricular hypertrophy and strain and intraventricular conduction defect. A plastic aortic valve was inserted and approximately 3 weeks later he was discharged home. He was extremely anxious and complained of recurrent episodes of dyspnea, vertigo, and numbness of the extremities and lips. Several months later he suddenly expired. At autopsy the heart weighed 1,150 Gm. with generalized cardiac enlargement and hypertrophy, particularly of the left ventricle. Severe aortic insufficiency of the rheumatic type was pathologically confirmed. The mitral valve showed no evidence of stenosis. The chordae tendineae were long and thin and inserted in the valve in the usual way. The papillary muscle, although moderately hypertrophied, appeared not remarkable.

Summary. As demonstrated in figure 2, this patient had the classical phonocardiographic and electrocardiographic findings of severe aortic insufficiency, in this instance of the rheumatic etiology. At the apex the typical findings associated with free aortic insufficiency were present: an ejection sound followed by a systolic murmur, a blowing diastolic murmur which occurred early in diastole between the second sound and ventricular diastolic gallop, and the diastolic rumble. The phonocardiograms demonstrate the 3 mur-

murs characteristically heard at the apex in patients with free aortic insufficiency: a systolic murmur, an early diastolic murmur (the aortic insufficiency diastolic blowing murmur which was transmitted to the apex), and the Austin Flint rumble. The loud ejection sound heard at the apex is often mistaken for a loud first sound, and the diagnosis of mitral stenosis may be incorrectly entertained.

Aortic Insufficiency with Associated Mitral Stenosis. In figure 3 are represented the phonocardiogram, electrocardiogram, and x-rays of a patient with a mild aortic insufficiency and associated mitral stenosis. The patient was a 52-year-old female with a known history of rheumatic fever. For 4 years she had been aware of dyspnea on exertion which had gradually progressed in the past 6 months. She had recently observed paroxysmal nocturnal dyspnea on a few occasions. Physical examination revealed a thin female in no acute distress. Pulse 75, grossly irregular. Blood pressure 180/80-70. There was moderate neck vein distention. The heart was enlarged to the left to the anterior axillary line. At the aortic area were heard a short, soft systolic murmur and a grade IV diastolic blowing murmur transmitted to the left sternal border. At the apex the first sound was accentuated and a prominent opening snap was heard. A grade IV diastolic rumble associated with a thrill was present. The second sound at the pulmonic area was accentuated. The liver was 3 fingerbreadths below the right costal margin and the tip of the spleen was palpable. There was no edema. The electrocardiogram revealed atrial fibrillation, left axis deviation, and T-wave changes consistent with left ventricular ischemia. The x-ray of the chest showed moderate transverse enlargement of the heart, suggesting an enlarged left ventricle. There was straightening of the left heart border, indicative of an increase in the size of the pulmonary artery segment and possibly left atrial appendage. On barium swallow there was posterior displacement and compression of the esophagus. The phonocardiogram confirmed the loud snapping first sound. A loud third sound was clearly recorded 0.12 second after the second sound. In our opinion, this third sound represents a delayed opening snap. Possibly, the opening snap of the mitral valve is delayed by an increase in early ventricular diastolic pressure which may decrease the pressure gradient between the left atrium and left ventricle. It is interesting to note that the opening snap has been "delayed" in all of our patients who have free aortic insufficiency and documented associated mitral stenosis. This patient's mitral valve orifice was estimated to be 1 cm.^{2} at the time of surgery.

Summary. This woman had the classic clinical picture of combined free aortic insufficiency and mitral stenosis. Her rhythm was atrial fibrillation and on auscultation she had a loud first sound, an accentuated pulmonic second sound, and a "delayed" opening snap. The diastolic rumble at the apex was loud and extended to the first sound. Chest x-ray and fluoroscopy revealed straightening of the left heart border and localized esophageal displacement consistent with left atrial enlargement.

Figure 4 represents a composite of 3 patients with proven free aortic insufficiency and associated significant mitral stenosis. Patient A was a 52-year-old female with rheumatic aortic insufficiency and mitral stenosis. The phonocardiogram showed a loud first sound, a prominent third sound, and a characteristic diastolic rumble. The rhythm was atrial fibrillation. The chest film showed transverse enlargement, suggesting left ventricular enlargement and straightening of the left heart border. Patient B was a 29-year-old male with a 2-year history of recurrent episodes of hemoptysis and progressive dyspnea on exertion. Blood pressure 160/70-0. At the apex were heard a grade II apical systolic murmur, an opening snap, and a rumbling murmur occupying practically all of diastole with presystolic accentuation. These auscultatory findings were confirmed by phonocardiogram. The chest x-ray revealed enlargement of the left ventricle and straightening of the left heart border. Enlargement of the left atrium and calcification in the mitral valve area were observed on fluoroscopy. The patient expired 6 days after cardiac surgery. Autopsy was performed and confirmed the clinical impression of rheumatic heart disease with moderate aortic insufficiency and severe mitral stenosis. The mitral valve was described as slightly larger than the diameter of a lead pencil. Patient C was a 35-year-old man with a history of several years of hemoptysis, progressive dyspnea on exertion, and fatigue. Physical examination revealed a blood pressure of 120/40-0. At the apex a grade III systolic murmur, an opening snap, and a grade IV diastolic rumble with presystolic accentuation were noted. These findings are documented on phonocardiogram. Notching of the P-waves on the electrocardiogram, suggestive of left atrial enlargement, was evident. Chest x-ray revealed enlargement of the left ventricle and slight straightening of the left heart border. At surgery the mitral valve was explored and moderate stenosis was found.

The 3 cases all demonstrate the accentuated first sound present when there is associated mitral stenosis. The third sound was easily recorded in all these patients, timing approximately 0.12 second after the second sound. The diastolic rumble usually filled all of diastole. In one patient the electrocardiogram showed atrial fibrillation and in another, broad-notched P-waves. In all cases there was definite straightening of the left heart border, suggestive of pulmonary artery segment and/or left atrial enlargement. As previously mentioned, these findings are in contrast to the patient with pure aortic insufficiency without associated mitral stenosis where the first apical sound is usually faint, the third sound occurs 0.14 to 0.16 second after the second sound (ventricular diastolic gallop), and the diastolic rumble is generally shorter and occurs in early and mid-diastole. The chest x-rays in these instances of aortic insufficiency alone do not reveal straightening of the left heart border.

Points of Confusion. In evaluating a number of patients with severe aortic insufficiency several points of confusion concerning the auscultatory findings have become apparent (fig. 5).

First, a loud ejection sound is frequently present over the base of the heart in patients with free aortic insufficiency. This may be heard quite well at the apex and may be misinterpreted as a loud first sound (fig. 5*A*). A gallop may be misinterpreted as an opening snap, and the Austin Flint murmur considered the murmur of organic mitral stenosis. The clinical points previously mentioned will help in making this differentiation. The phonocardiogram is also helpful, since the ejection sound may occur at a time later than that of the first sound.

Second, in some patients (fig. 5*B*) both an opening snap and ventricular diastolic gallop may be present. If this is recognized, one may suspect the presence of organic mitral stenosis. The presence of an early ventricular diastolic gallop would seem clinically to preclude a tight mitral stenosis. Figure 5*C* presents a woman with a tight mitral stenosis and a Graham Steell murmur. In some instances the Graham Steell murmur may be grade III or even grade IV, and confused with the murmur of aortic insufficiency. In our experience the Graham Steell murmur, except when extremely loud (grade IV), is seldom heard at the aortic area and is usually heard only in the pulmonic area and along the left sternal border. The presence of a well-maintained diastolic blood pressure would

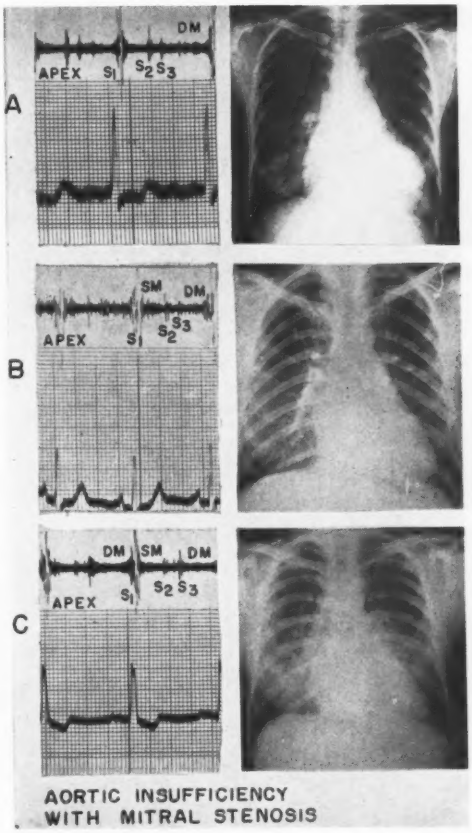

FIG. 4. Composite of 3 patients with aortic insufficiency and associated significant mitral stenosis. Note the loud first sound (S_1) "delayed" opening snap, (S_3),* and pan-diastolic rumble in all instances. The cardiac silhouettes all show some straightening of the left heart border.

*Ed.: The use of the designation "S_3" for opening snap is liable to occasion confusion since the more general practice is to use "S_3" for third heart sound or ventricular gallop. Sometimes in mitral valve disease both an opening snap and a third heart sound are present. Figure 4*C* may be cases in point: there appears to be an opening snap between S_2 (which is slightly split) and the third sound (labeled S_3). The identity—whether opening snap or gallop—of the components labeled S_3 is not always clear.

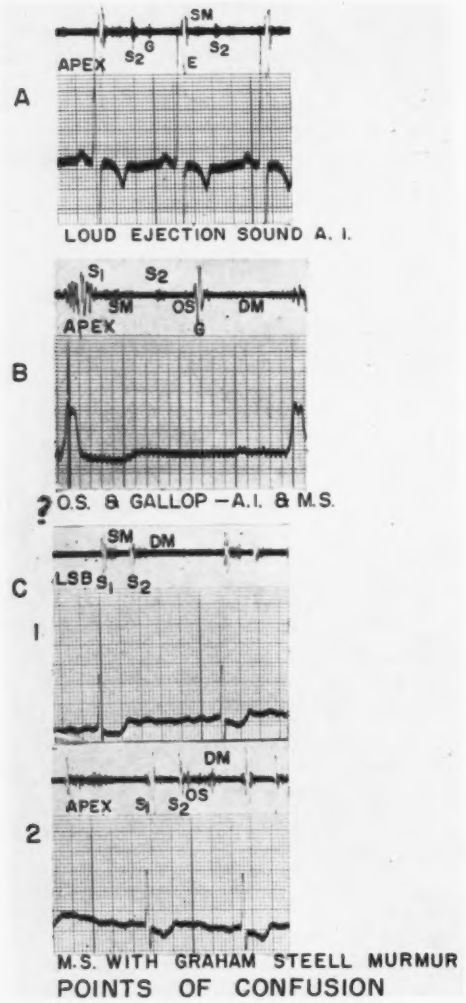

FIG. 5. Auscultatory points of confusion. In patient A, the loud ejection sound (*E*) was mistaken for a loud first sound and therefore the patient was suspected of having associated mitral stenosis. Patient B demonstrates possibility of both an opening snap (*OS*) and a ventricular diastolic gallop (*G*). Clinically, the patient had moderately free aortic insufficiency and significant mitral stenosis confirmed by surgery. Patient C had classical tight mitral stenosis with a loud Graham Steell murmur misdiagnosed as that of aortic insufficiency. She had none of the peripheral signs of free aortic insufficiency. At the apex note the loud first sound (*S*.), opening snap (*OS*), and diastolic rumble (*DM*).

be a point against any significant aortic i- sufficiency, although certainly mild aor- insufficiency may occur with a fairly norm- diastolic pressure. If the patient has t- classic findings of tight mitral stenosis wi- a loud pulmonic second sound, a normal dia- tolic pressure, and a decrescendo blowi- diastolic murmur best heard in the pulmon- area and along the left sternal border, th- one can assume that this is a Graham Ste- murmur and not the murmur of aort- insufficiency.

When the heart rate is rapid (90 or abov- one is more apt to misdiagnose mitral stenos- when only free aortic insufficiency is presen- since the diastolic rumble frequently occupi- all of diastole, often with presystolic accentua- tion. A patient with aortic insufficiency hav- ing normal sinus rhythm, a rapid heart rat- and a short P-R interval might be particularly confusing. In this instance the short P-R interval would produce accentuation of the first sound leading to confusion with the loud first sound of mitral stenosis.

It has often been stated in the literature that in organic mitral stenosis the Q-1 interval is prolonged, and we have attempted in some instances to utilize this fact to differentiate which patients have associated mitral stenosis.[6, 7] In our experience, in patients with free aortic insufficiency, the first sound is often quite indistinct and difficult to clearly define on the phonocardiogram. Also, one may mistake the loud systolic ejection sound with the first sound, and thereby misinterpret a prolonged Q-1 interval. For these reasons we have not made clinical application of the Q-1 interval.

Mechanisms of Productions of the Austin Flint Murmur. Several mechanisms have been proposed for production of the Austin Flint murmur, although in general all are based on the concept of the production of relative mitral stenosis.[1, 2, 4, 8, 9] Possibly the regurgitant aortic stream may displace the aort- leaflet of the mitral valve so that this leafl- encroaches on the mitral orifice during dia- tole, producing some narrowing. The passa-

of blood through a relatively normal mitral valve into a large dilated left ventricle may also act as a relative mitral stenosis. In addition, some investigators believe that the regurgitant aortic stream may, by increasing left ventricular diastolic pressure, displace the mitral leaflets upward toward a more closed position. The presence of mitral insufficiency would also tend to increase the flow across the mitral valve, since during systole some of the blood from the left ventricle would regurgitate into and distend the left atrium, producing both an increase in left atrial volume and pressure. In diastole, this would result in increased velocity and quantity of blood traversing the mitral orifice, again contributing to a relative mitral stenosis.

Acknowledgment

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References

1. Flint, A.: On cardiac murmurs. Am. J. M. Sc. **44**: 29, 1862.
2. Thayer, W. S.: Observations on the frequency and diagnosis of the Flint murmur in aortic insufficiency. Am. J. M. Sc. **122**: 538, 1901.
3. White, P. D.: A note on the differentiation of the diastolic murmurs of aortic regurgitation and mitral stenosis. Boston M. & S. J. **195**: 1146, 1926.
4. Currens, J. H., Thompson, W. B., Rappaport, M. B., and Sprague, H. B.: Clinical and phonocardiographic observations on the Flint murmur. New England J. Med. **248**: 583, 1953.
5. Luisada, A. A., Haring, O. M., and Zilli, A. B.: Apical diastolic murmurs simulating mitral stenosis: II. Graphic differentiation. Ann. Int. Med. **42**: 644, 1955.
6. Wells, B. G.: The graphic configuration of apical diastolic murmurs. Brit. Heart J. **14**: 261, 1952.
7. Kelly, J. J.: Diagnostic value of phonocardiograpy in mitral stenosis. Mode of production of first heart sound. Am. J. Med. **19**: 862, 1955.
8. Herrmann, G. R.: The Austin Flint phenomenon. Am. Heart J. **1**: 671, 1926.
9. Gouley, B. A.: The aortic valvular lesion associated with the Austin Flint murmur. Am. Heart J. **22**: 208, 1941.

Auscultatory Findings in Pericardial Effusion and in Ventricular Aneurysm

By W. Proctor Harvey, M.D., and John P. Mandanis, M.D.

BOTH heart sounds may be markedly diminished in the presence of a large pericardial effusion.[1-3] On the other hand, with a pericardial effusion of moderate size, the heart sounds maintain normal intensity. Likewise, the x-ray and electrocardiogram may not show typical changes. In such cases angiocardiography is sometimes used for diagnosis; sometimes a diagnostic pericardial aspiration is attempted with an exploratory needle, or direct operative exploration is performed.

A useful sign in selected cases of pericardial effusion has been the effect of position on intensity of heart sounds. In normal individuals, as shown in figure 1, heart sounds remain the same or become louder when the subject turns on his stomach. When the patient turns on his stomach auscultation is easier and more convenient if the patient props himself up on his elbows. The heart sounds may become louder, presumably, because the heart is in closer proximity to the chest wall, and in turn, to the stethoscope. On the other hand, in some cases of pericardial effusion, as illustrated in figure 2 (*top*), the heart sounds became fainter instead of remaining the same or becoming louder. In one case the diagnosis of pericardial effusion was not evident at that particular time by the usual clinical evaluation, but subsequently there developed typical signs of pericardial effusion which was verified at post mortem examination when a tumor involving the pericardium was found.

The sign was most useful in the case of a 45-year-old woman with rheumatic mitral stenosis and insufficiency, aortic stenosis and insufficiency, and tricuspid insufficiency (fig. 2). The heart was enlarged as a result of the valvular lesions and the patient's clinical condition was noted to be steadily worsening. The possibility of pericardial effusion arose, but could not be established by x-ray or fluoroscopic examination, or electrocardiogram. On turning the patient from her back to her abdomen, the heart sounds and murmurs were noted, and demonstrated on the phonocardiogram, to significantly decrease. Her condition continued to deteriorate, and approximately 1 week later the heart, by x-ray, had significantly increased in size and the silhouette was now suggestive of pericardial effusion. Under direct vision in the operating room, approximately 1,000 ml. of bloody fluid was removed from the pericardial cavity. Following this, her condition improved

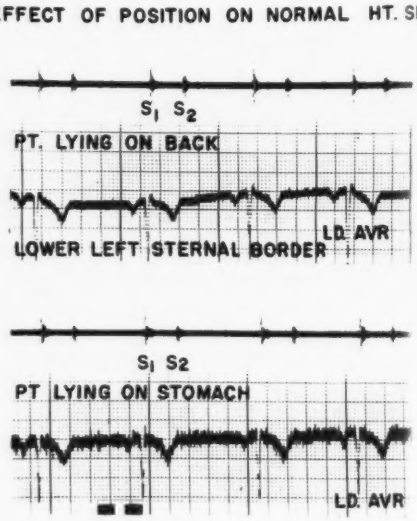

Fig. 1. Healthy young physician with no heart disease. Heart sounds (S_1, S_2) remained same on change of position.

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Supported in part by grants from the Washington Heart Association and the Metropolitan Heart Guild, Washington, D. C.

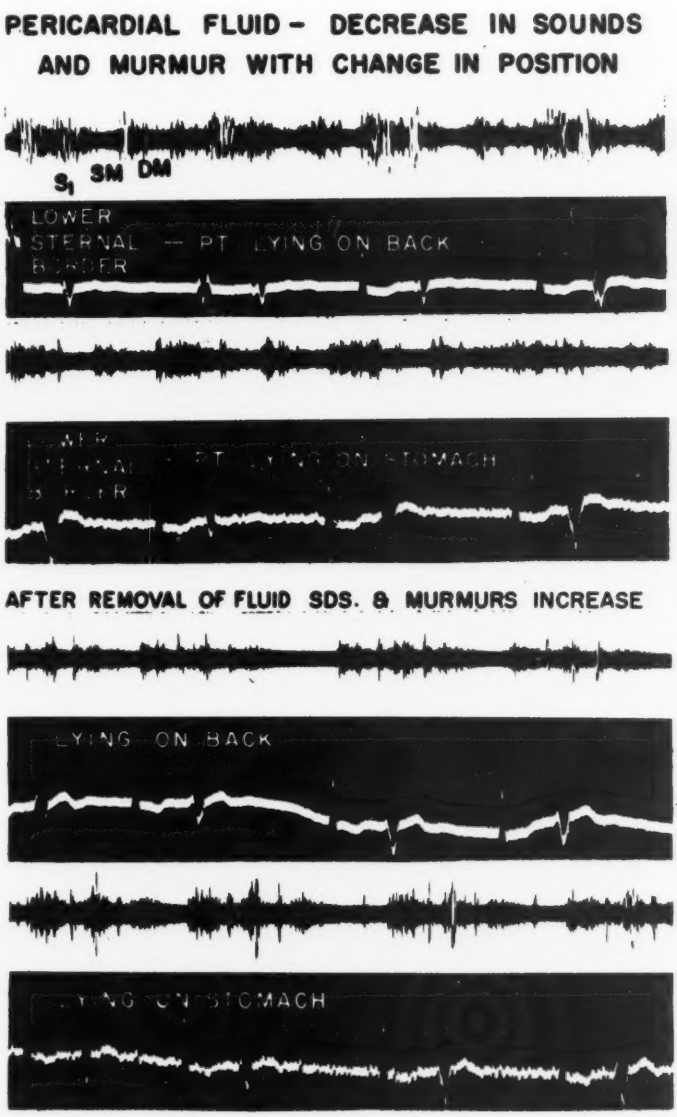

FIG. 2. A 45-year-old woman with combined rheumatic aortic and mitral valvular lesions. *Upper Two Tracings.* Pericardial effusion present. Note decrease in sounds and murmurs on change of position from back to stomach. *Lower Two Tracings.* No effusion. Sounds and murmurs now increase with position change.

and 2 weeks later, as shown in the phonocardiogram (fig. 2, *lower tracings*), the effect of position on her heart sounds and murmurs was again tested. This time, as noted, there was a definite increase in both sounds and murmurs coincident with the patient's turning to her abdomen.

Auscultatory evidence of pericardial effusion is variable, however. Often patients having the largest effusions show little change

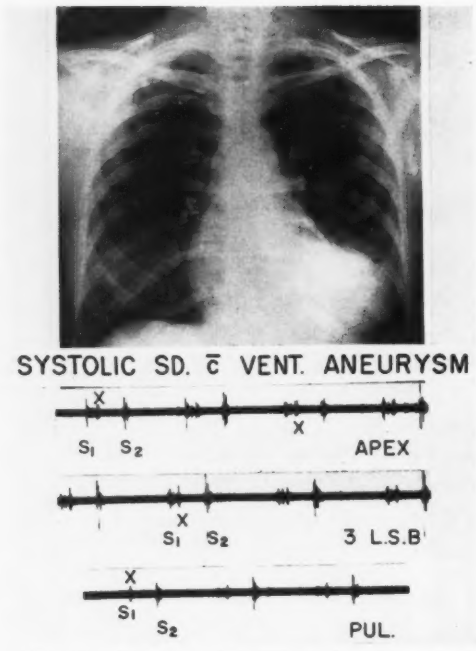

FIG. 3. A 50-year-old woman with aneurysm of the left ventricle resulting from a previous myocardial infarction. Note aneurysm shown on the x-ray which produced an early systolic sound (*X*) as shown on phonocardiograms. The sound coincided with a prominent localized systolic impulse palpated at the apex.

with position. It is postulated that with the more moderate amounts of effusion, coincident with change in patient's position from flat to the abdomen, more fluid is interposed between the heart and the stethoscope, thereby decreasing sounds and murmurs. On the other hand, with the larger effusions already greatly distending the pericardial sac, there may be little change, and in fact in some instances even an increase has been noted in such cases. However, the diagnosis with the largest effusions present no diagnostic problem. Here both heart sounds are faint in both positions, and the electrocardiogram shows voltage on the lower side of normal. Likewise, with smaller effusions there may be little change in intensity of the murmur coincident with change in position. A false positive sign is elicited in the presence of pleural fluid which, if present, may in some cases cause a decrease in intensity of heart sounds when the patient is lying on his stomach.

SYSTOLIC SOUND WITH VENTRICULAR ANEURYSM

In many cases postinfarctional ventricular aneurysm is overlooked and the diagnosis is made only at post mortem examination. It has been stated that there are no constant and characteristic auscultatory findings of ventricular aneurysm, although a "weak" or "muffled" first heart sound, gallop rhythm, systolic or diastolic murmurs, or both, have been described.[4-8] More commonly, an impulse on palpation coincident with systole has been mentioned.

Figure 3 represents a woman with proven ventricular aneurysm as a result of previous myocardial infarction. On auscultation the striking feature in this case was the presence of an apical systolic sound occurring in the first third of systole coincident with a prominent systolic impulse which was readily palpated in a localized spot over the apex. This patient, likewise, had electrocardiographic changes as well as fluoroscopic and x-ray evidence of aneurysm of the left ventricle. She underwent surgery for ventricular aneurysm, and although it was not excised, the weakened area was reinforced by the surgeon.

This systolic sound has been observed in other cases of ventricular aneurysm. This sound in systole corresponding to a localized palpable systolic impulse occurring in a patient with a history of coronary artery disease or old myocardial infarction, may be a valuable auscultatory clue. The sound is most likely produced by the paradoxical systolic bulge (or expansion) of the localized aneurysmal area striking against the chest wall. As to whether this systolic sound will be present or not, will depend naturally upon the location of the aneurysm and the extent of involvement.

REFERENCES

1. FRIEDBERG, C. K.: Diseases of the Heart. Ed. 2. Philadelphia, W. B. Saunders Company, 1956, p. 593.
2. LEVINE, S. A., AND HARVEY, W. P.: Clin

Auscultation of the Heart. Ed. 1. Philadelphia, W. B. Saunders Company, 1949.
3. Wood, P.: Diseases of the Heart and Circulation. Ed. 2. Philadelphia, J. B. Lippincott Company, 1956, p. 661.
4. Chlichter, J., Hellerstein, H. K., and Katz, L. N.: Aneurysm of the heart: A correlative study of one hundred and two proved cases. Medicine **33**: 43, 1954.
5. Takil, R. J.: Ventricular aneurysms of the heart. Am. Heart J. **49**: 934, 1955.
6. Crawford, J. H.: Aneurysm of the heart. Arch. Int. Med. **71**: 502, 1943.
7. Scherf, D., and Brooks, A. M.: The murmurs of cardiac aneurysm. Am. J. M. Sc. **218**, 389, 1949.
8. Moyer, J. B., and Hiller, G. I.: Cardiac aneurysms: Clinical and electrocardiographic analysis. Am. Heart J. **41**: 340, 1951.

Mammary Souffle of Pregnancy

Report of Two Cases Simulating Patent Ductus Arteriosus

By JAMES T. SCOTT, M.B., M.R.C.P., AND EDMOND A. MURPHY, M.D.

Little attention has been paid to the continuous parasternal murmur that may occur during pregnancy and that disappears after lactation. We have encountered 2 cases of this phenomenon. The murmur probably arises from arteries supplying the breast. The mechanism of its production has not been established, but it may depend on some permanent anatomic anomaly. This benign murmur has special characters by which it may be readily distinguished from significant continuous murmurs.

SINCE Gibson's classical paper[1] the "machinery" murmur has been recognized as the cardinal physical sign in the diagnosis of patent ductus arteriosus. Indeed, Muir and Brown[2] described it, in its most typical form, as "the most pathognomonic of all murmurs." Owing largely to the stimulating effect of surgery upon diagnostic precision, however, there have been brought to light several other conditions producing continuous murmurs more or less similar in character. Conditions that produce such murmurs may be grouped as follows: 1. Patent ductus arteriosus. 2. Aortic-pulmonary septal defect.[3, 4] 3. Arteriovenous fistulas, whether congenital defects,[5] secondary to acquired disease,[6] or surgically constructed.[7] 4. Dilated arteries, as in the collateral circulation in coarctation of the aorta,[6, 8] or that in pulmonary atresia.[9] 5. Venous hums. Palmer and White[10] frequently found these near the sternum in normal children. Venous hums in cirrhosis of the liver are sometimes confined to the midline of the chest and have occasionally been confused with the murmurs of congenital heart disease.[11, 12] 6. Anomalous drainage of a coronary artery into the right ventricle.[13, 14] Similarly, rupture of the sinus of Valsalva into the right ventricle may produce a continuous murmur.[15] 7. Stenosed branch of the pulmonary artery with poststenotic dilatation[16] or multiple stenoses of the branches of the pulmonary artery.[17] 8. Anomalous pulmonary venous return.[18] 9. Various other combinations of congenital defects, such as high ventricular septal defect and aortic or pulmonary valvular incompetence, in which something like a continuous murmur may be heard, the mechanism of production being more obscure.[8] 10. The aortic arch syndrome, in which a continuous murmur may be heard, probably due either to a high pressure gradient along stenosed arteries, or to dilated collateral vessels. In Ross and McKusick's series[19] the continuous murmur, heard in 5 cases, was in every instance supraclavicular. 11. Pregnancy. Innocent systolic murmurs, frequent at any time, are commonly heard all over the base of the heart in pregnancy; functional diastolic murmurs in pregnancy are mentioned by some writers.[20–24] We have found few references to murmurs continuous in character during pregnancy[8, 26, 27] and for this reason report the following cases.

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CASE REPORTS

Case 1. L.C., a 31-year-old Negro woman, was seen in the twenty-second week of her fifth pregnancy.

There was a past history of meningitis in childhood, latent syphilis treated with penicillin in 1950, and salpingitis in 1952. Of her 4 previous pregnancies, 2 had resulted in normal deliveries, 1 in a miscarriage, and 1 in a tubal pregnancy for which a salpingectomy was performed. There was no history of heart disease, and at all of her many previous physical examinations the heart had been described as normal. There was no family

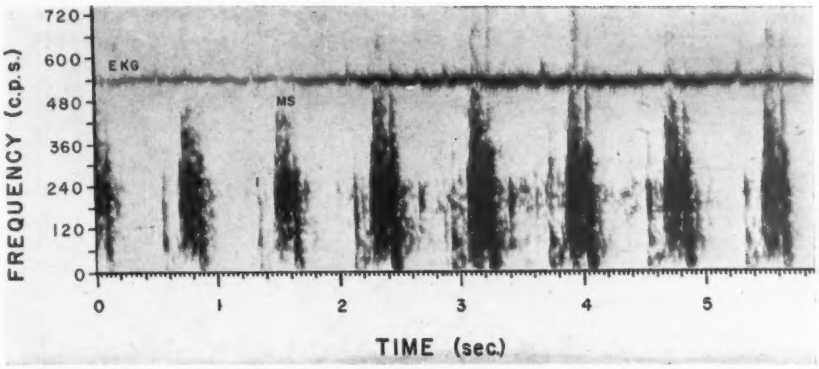

FIG. 1. Case 1. Taken from the second right intercostal space. The souffle (*MS*) in this instance was not continuous. Note the gap between the first sound (*1*) and the onset of the murmur.

history of heart disease. The patient was now symptom-free, having in particular no dyspnea or other symptom referable to the cardiovascular system.

Examination showed a healthy-looking pregnant woman with the uterus enlarged to the level of the umbilicus. The pulse was regular at 88, and the blood pressure was 100/50 mm. Hg. The jugular venous pressure was not raised and there was no edema. The femoral pulses were easily palpable and not delayed. The apex beat was palpable 13 cm. from the midline in the fifth left intercostal space. No thrills were felt. The second pulmonary sound was accentuated but not widely split.

Localized to the second left interspace, close to the sternum, was a harsh "machinery" murmur heard continuously throughout systole and diastole. The murmur was not constant, but came and went with no relationship to posture, movement, or respiration. The effects of the Valsalva maneuver were not noted. Sometimes only the diastolic component was missing, and at other times the whole murmur was absent, in which case a soft systolic murmur of quite different character was heard in the second left interspace. It was noted, however, that the harsh continuous murmur was always abolished by firm pressure with the stethoscope.

General physical examination was otherwise negative. Chest x-ray showed an elevated diaphragm with a transverse heart and prominent pulmonary conus, normal for a pregnant woman. An electrocardiogram was normal. The hematocrit value was 36 per cent.

The patient was seen several times before and immediately after her normal delivery in December 1956 and on all but one occasion the continuous murmur was present. It was found to be variable in position, for while it was usually localized to the second left interspace, it was sometimes heard in the third left interspace or in corresponding situations on the right side. Disappearance of the murmur on pressure was invariably observed.

Two days after delivery a spectral phonocardiogram[21] was taken through the courtesy of Dr. Victor McKusick (figs. 1, 2). In these records, frequency in cycles per second is on the vertical axis, time in seconds on the horizontal axis, and intensity at any given point in time and at a given frequency is indicated by grade of blackness in that part of the record.

The patient breast-fed her baby for 2 weeks only. She was again seen 4 months after delivery. The blood pressure was 120/75 mm. Hg, the apex beat was 9 cm. from the midline, the heart sounds were quite normal, and careful search revealed no trace of the murmur.

Case 2. N.C., was a Negro woman with no history of previous illness and no family history of congenital heart disease.

During her first pregnancy at the age of 13 the heart was described as normal. Her second pregnancy occurred in 1951 at the age of 16, and at the twenty-first week a cardiac murmur was first discovered. It was described on one occasion as heard all over the base of the heart, very loud, high pitched, systolic and diastolic in timing, and accompanied by a thrill in the second left interspace. On another occasion it was described as a systolic murmur over the second left interspace. An electrocardiogram was normal, and fluoroscopy showed elevation of the diaphragm due to pregnancy, with equivocal enlargement of the left atrium. The patient was considered to have congenital heart disease, probably patent ductus or atrial septal defect, and cardiac catheterization

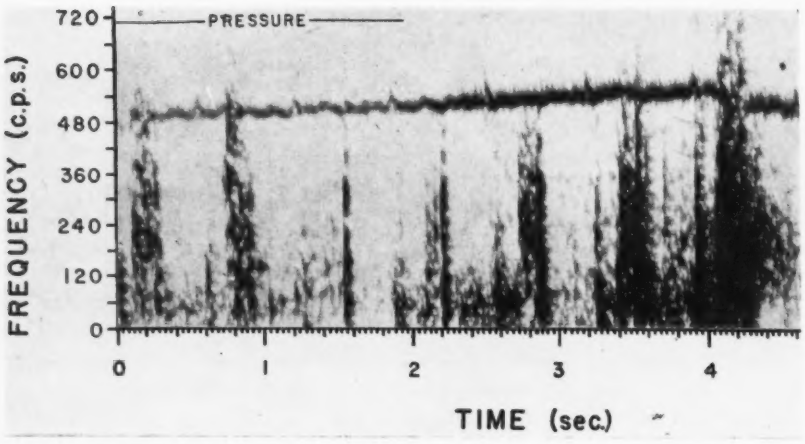

FIG. 2. Case 1. Taken from the second left interspace. When pressure was applied, the murmur was almost obliterated. In the second half of the tracing, the pressure was released and the murmur became continuous.

was contemplated. After delivery, breast feeding was not attempted, and a month later no abnormality was found, there being only a soft apical systolic murmur. The patient remained symptom-free.

We saw her for the first time when she was 22 years old and in the twentieth week of her third pregnancy. Examination showed a healthy looking pregnant woman. The pulse was regular at 80, and the blood pressure was 110/70 mm. Hg. The jugular venous pressure was not raised, and there was no edema, or hepatic or splenic enlargement. The femoral pulses were palpable and not delayed. The heart was not enlarged clinically, and there were no thrills. The second pulmonary sound was slightly accentuated but not abnormally split.

In the second and third left and right spaces there was a loud harsh high-pitched murmur heard throughout systole and extending into the first half of diastole. The murmur varied in site from minute to minute, being sometimes best heard to the left of the sternum and sometimes to the right. The diastolic component was not constantly present, and the murmur was not heard continuously throughout systole and diastole (as it was in case 1) except when slight pressure was exerted with the stethoscope. Firm pressure abolished the murmur.

Movement of the head did not affect the murmur, but (again in contrast to case 1) the murmur was not audible when the patient sat up. This postural effect was not due to the exertion of sitting up, because the murmur remained absent no matter how long the patient remained sitting at rest. When she again lay down, the murmur reappeared after an interval of about half a minute.

A Valsalva maneuver was carried out several times, and the following events were noticed on each occasion: during the first 2 or 3 beats the murmur became progressively louder until it acquired a roaring character; after 4 or 5 more beats it declined in intensity, becoming softer than before the breath was held. Even when the murmur was at its loudest during this procedure, it was immediately abolished by firm pressure. Routine investigation revealed a negative serological test for syphilis and a hematocrit of 33%.

The patient was again seen at the twenty-fifth week of pregnancy, and the characters of the murmur were unchanged. A spectral phonocardiogram taken at that time is shown in figure 3. She was seen at 1 and 2 months after delivery. On both occasions the murmur was persistently absent.

DISCUSSION

Morgan Jones[24] mentioned that loud, harsh, extracardiac systolic murmurs, sometimes extending into diastole, may be heard in pregnancy; and that such murmurs have a very distinctive musical quality, and are heard at unusual sites and in unusual phases of the cardiac cycle. Gilston and McPhaul[26] described 2 pregnant patients in whom both systolic and diastolic murmurs were present in the absence of recognizable organic disease.

This l l them to examine a further group of health pregnant women in several of whom they countered continuous murmurs (no numb s were given for these). Grant[27] describe 2 cases of pregnancy in one of which a syst ic murmur continued into diastole and in th other a systolic murmur only, at first sugge ing a diagnosis of patent ductus arteriosus In these last 2 papers it was noted that ch murmurs disappeared on pressure. Bonh n Carter and Walker[8] stated that a conti ious murmur is not infrequently heard on au cultation of the lactating breast.

Th following characters of the murmur are mphasized. It may occur throughout systol and diastole and its quality may closely simulate that of patent ductus arteriosus. The distinguishing properties of the sound are its variation in position from time to time, its evanescence, and its disappearance on firm pressure with the stethoscope. We found no way of bringing back the murmur when it was absent, and in neither of our cases was it affected by altering the position of the head or by the phase of respiration. The continuous character of the murmur was, in our second case, accentuated by light pressure with the stethoscope. Indeed, we have encountered another case in which a similar murmur, inaudible on routine auscultation, was produced by light, but not by firm, pressure. Such a murmur, however, would not be mistaken for that of patent ductus.

The onset of the murmur during pregnancy, its disappearance afterwards, and its abolition by firm pressure indicate that it arises from superficial vessels supplying the lacta ing breast. The failure of the Valsalva manc uver to abolish the murmur suggests an arte al rather than a venous origin. Such a vi w is further supported by the phonocardiog ms which show that the maximum intensi y is during systole; at times no diastolic com ponent is recognized. In contrast, venous hum have a diastolic accentuation. The gap obse ed between the first heart sound and the c mmencement of the murmur is also characte stic of an arterial origin.

W have had no opportunity to study the behavior of the murmur during lactation, and whether the murmur disappears soon after delivery or only after all lactation has ceased. In Grant's cases[27] the murmur disappeared "soon after lactation began." We do not know whether pregnancy produces this murmur by virtue of the associated increased blood flow through the breast, by engorgement of the breast with milk or blood, or by some other effect such as mechanical distortion of vessels by elevation of the diaphragm. Grant's observations favor one of the latter two possibilities, because active hyperemia presumably persists throughout lactation. Since, however, the murmur is found in only a minority of pregnancies, and yet occurred in 2 successive pregnancies in our second case, there may be some further factor in its production, perhaps a latent structural anomaly in branches of the internal mammary arteries. The mechanism of production of this sound is comparable to that of the uterine souffle, and it seems appropriate to apply to it the analogous term "mammary souffle." It is possible that the low hematocrit encountered in both cases is necessary for the production of the murmur, but it cannot be the main cause since such degrees of anemia are usually in pregnancy. As a test of this, we analyzed the routine hematocrit readings from a random sample of 50 colored women who were

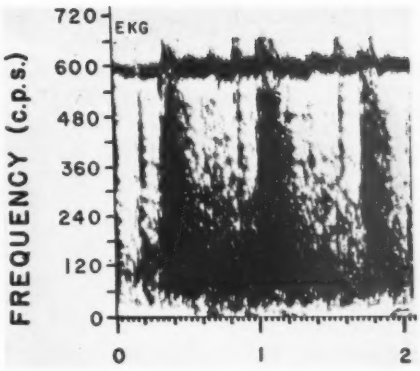

FIG. 3. Case 2. Taken from the second left interspace. This continuous murmur was loudest and contained higher frequency components near the second sound.

between the eighteenth and thirtieth weeks of their third and fourth pregnancies. These readings were taken from current case records of the Johns Hopkins Hospital. The following results were obtained.

Median 33.3 per cent

Range 27.5 to 39.0 per cent

Mean 33.6 per cent

Mean ± two standard deviations 28.3 to 39.0 per cent

In both of our patients, the hematocrit lay close to the above mean.

The resemblance on superficial examination between this murmur, when continuous, and that of patent ductus arteriosus may lead to diagnostic error, especially since there are further points of similarity in the hemodynamic effects of the 2 conditions—high pulse pressure, accentuation of the pulmonary second sound, and prominence of the pulmonary artery radiologically. The absence of symptoms is of little significance, since it is so characteristic in uncomplicated patent ductus as to be classed as one of its diagnostic criteria.[2]

Espino-Vela and Castro-Abreu,[28] in a series of 53 cases of congenital heart disease in pregnant women, encountered patent ductus in 28 instances. Though it is clear from this and many other reports that the association of patent ductus and pregnancy is not rare, it is conceivable that some such cases have been misdiagnosed. The 2 murmurs are, however, readily distinguishable by the features mentioned. We are in no position to comment on the frequency of this phenomenon.

Summary

The causes of continuous murmurs in the chest are listed. Two cases are reported of a continuous murmur occurring during pregnancy, disappearing after lactation, probably arising from superficial arteries supplying the lactating breast, and for that reason called a "mammary souffle." Its quality may closely resemble that of the murmur of patent ductus arteriosus, from which it can be distinguished by its changeability in position, its evanescence, and its disappearance on firm pressure.

Acknowledgment

It is a pleasure to acknowledge the help of Dr. Victor McKusick in the preparation of this paper.

Summario in Interlingua

Es presentate un lista del causas de murmures continue in le thorace. Es reportate duo casos de murmures continue que occurreva durante le pregnantia, dispareva post le fin del periodo de lactation, e esseva probabilemente causate in arterias superficial que provisionava le mammas lactante. Pro iste ration, le termino "sufflo mammari" es usate pro illos. Le qualitate del sufflo pote esser multo simile al murmure de patente ductus arteriose, ab que illo es distinguibile per le variabilitate de su position, per su evanescentia, e per le facto que illo dispare sub forte pression.

REFERENCES

1. Gibson, G. A.: Clinical lectures on circulatory affections. Lecture 1. Persistence of the arterial duct and its diagnosis. Edinburgh M. J. **8**: 1, 1900.
2. Muir, D. C., and Brown, J. W.: Congenital heart disease. Brit. M. J. **1**: 966, 1935.
3. Gasul, B. M., Fell, E. H., and Casas, R.: The diagnosis of aortic septal defect by retrograde aortography: Report of a case. Circulation **4**: 251, 1951.
4. Gibson, S., Potts, W. J., and Langewisch, W. H.: Aortico-pulmonary communication due to localized congenital defect of the aortic septum. Pediatrics **6**: 357, 1950.
5. Johnson, J. B., Jordan, A., and Lawlah, J. W.: Arteriovenous fistula simulating patent ductus arteriosus. Evaluation by venous catheterization and angiocardiography. J.A.-M.A. **155**: 1408, 1954.
6. White, P. D.: Heart Disease. Ed. 4. Macmillan, New York, 1951, p. 342.
7. Blalock, A., and Taussig, H. B.: The surgical treatment of malformations of the heart in which there is pulmonary stenosis or pulmonary atresia. J.A.M.A. **128**: 189, 1945.
8. Bonham Carter, R. E., and Walker, C. H. M.: Continuous murmurs without patent ductus arteriosus. Lancet **1**: 272, 1955.
9. McKusick, V. A.: Personal communication.
10. Palmer, R. S., and White, P. D.: A note on the continuous humming murmur heard in the supra and infraclavicular fossae and over the manubrium sterni in children. New England J. Med. **199**: 1297, 1928.

11. [illegible]YN, N. B.: On some venous murmurs found in hepatic cirrhosis and their confusion with murmurs of congenital heart disease. Am. J. M. Sc. **180**: 525, 1930.

12. [illegible]AYER, W. S.: On the presence of a venous hum in the epigastrium in cirrhosis of the liver. Am. J. M. Sc. **141**: 313, 1911.

13. [illegible]AVIS, C., DILLON, R. F., FELL, E. H., AND GASUL, B. M.: Anomalous coronary artery simulating patent ductus arteriosus. J.A.M.A. **160**: 1047, 1956.

14. [illegible]ALTHER, R. J., STARKEY, G. W. B., ZERVOPOLUS, E., AND GIBBONS, G. A.: Coronary arteriovenous fistula. Am. J. Med. **22**: 213, 1957.

15. [illegible]AUSSIG, H. B.: Congenital Malformations of the Heart. New York, The Commonwealth Fund, 1948, p. 344.

16. [illegible]UNNING, A. J.: An unusual case of a continuous murmur simulating persistent ductus arteriosus and associated with other congenital cardiac defects. Thorax **12**: 34, 1957.

17. ARVIDSSON, H., KARNELL, J., AND MÖLLER, T.: Multiple stenosis of the pulmonary arteries associated with pulmonary hypertension, diagnosed by selective angiocardiography (Case 1). Acta radiol. **44**: 209, 1955.

18. KEITH, J. D., ROWE, R. D., VLAD, P., AND O'HANLEY, J. H.: Complete anomalous pulmonary venous drainage. Am. J. Med. **16**: 23, 1954.

19. ROSS, R. S., AND MCKUSICK, V. A.: Aortic arch syndromes: Diminished or absent pulses in arteries arising from arch of aorta. Arch. Int. Med. **92**: 701, 1953.

20. JENSEN, J.: The Heart in Pregnancy. St. Louis, C. V. Mosby Co., 1938.

21. GAMMELTOFT, S. A.: The heart in pregnancy. Surg. Gynec. & Obst. **46**: 382, 1928.

22. MUSSER, J. H.: Heart disease in pregnancy. Am. J. M. Sc. **193**: 121, 1937.

23. SODEMAN, W. A.: Cardiac changes in pregnancy unrelated to the usual etiological types of heart disease. Am. Heart J. **19**: 385, 1940.

24. JONES, A. M.: Heart Disease in Pregnancy. London, Harvey and Blythe, Limited, 1951, p. 11.

25. MCKUSICK, V. A., TALBOT, S. A., AND WEBB, G. N.: Spectral phonocardiography: Problems and prospects in the application of the Bell sound spectrograph to phonocardiography. Bull. Johns Hopkins Hosp. **94**: 187, 1954.

26. GILSTON, R. J., AND MCPHAUL, J. J.: Physiologic murmurs in pregnancy: A reemphasis. Med. Ann. District of Columbia **24**: 461, 1955.

27. GRANT, R. P.: A precordial systolic murmur of extracardiac origin during pregnancy. Am. Heart J. **52**: 944, 1956.

28. ESPINO-VELA, J., AND CASTRO-ABREU, D.: Congenital heart disease associated with pregnancy. Am. Heart J. **51**: 542, 1956.

The "Normal" Systolic Murmur

By DALE GROOM, M.D.

THE presence of functional systolic murmurs in some adults has long been recognized. Of recent interest is the finding that systolic murmurs are actually present in virtually all normal subjects.

By means of a technic already described,[1] utilizing a high-sensitivity heart sound pickup in a soundproof room, systolic murmurs were recorded from the precordium of 100 per cent of 36 medical student volunteers. In none of these subjects had a murmur been described previously, nor was one audible on ordinary stethoscopic auscultation. The point of maximum intensity of the murmur in nearly all instances was located along the left sternal border in the second, third, or fourth intercostal space. Intensity of the murmur varied in some subjects from day to day or with different phases of respiration or changes in position, and with exercise. Similar systolic murmurs were found to be present in most fetal heart sound recordings during the last trimester of gestation.

The exact mechanism of origin of such murmurs in the adult is uncertain. Their presence is understandable, however, on the basis of what is now known of circulatory dynamics, and it appears that they represent a universal functional murmur which is usually subaudible.

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Supported by grants from the South Carolina Heart Association and the National Heart Institute.

REFERENCE

1. GROOM, D.: A high sensitivity pickup for cardiovascular sounds. Am. Heart J. 54: 592, 1957.

ADDENDUM

In order to meet publication schedules, the first pages of this Symposium went to press before the acknowledgments on page 946 could be completed. The listing of aid should also have included contributions from the Upjohn Co., and from Hoffmann-La Roche, Inc.

ABSTRACTS

ATHEROSCLEROSIS

Holman, R. L., McGill, H. C., Jr., Strong, J. P., and Geer, J. C.: The Natural History of Atherosclerosis. The Early Aortic Lesions as Seen in New Orleans in the Middle of the 20th Century. Am. J .Path. **34**: 209 (March-April, 1958.

The authors have analyzed the aortas from 526 autopsies conducted on individuals between the ages of 1 and 40 years who died at Charity Hospital and some who died of unknown cause in New Orleans and came under the jurisdiction of the Coroner of that city. All the aortas were examined grossly and after staining with Sudan IV. The fatty streaks, fibrous plaques, and lesions in the fibrous plaques, such as hemorrhage, ulceration, thrombosis, and calcification, were estimated for each aorta on the basis of intimal surface involved. An analysis of these changes was then made and very interesting and statistically significant results were obtained. Fatty streaks are not caused by terminal acute illness, nor are they lessened by terminal acute illness. All patients 3 years of age or older in this series had some fatty intimal deposits and the percentage of involvement rose slowly until the age of 8. At that time the extent of lesions increased greatly in the Negro and for the next 5 years the rise was very great. The white individuals followed the Negro pattern, but delayed by about 5 years. Negro males and females were very much alike, but the greatest involvement was in the females of comparable age. Fibrous plaques occur at about the age of 20, and increase appreciably in the fourth decade. About 15 years elapse between the appearance of fatty streaks and the conversion of these into fibrous plaques. The aortic ring is the first region involved. The descending thoracic and abdominal portions develop lesions between the ages of 8 and 18. None of the data support any thought that dietary factors are in any way related to the pathogenesis of atherosclerosis. The rapid rise of the atherosclerotic changes in the years of puberty suggests hormonal activity as a decidedly important factor in the pathogenesis of these lesions.

HARVEY

Keys, A., Kimura, N., Kusukawa, A., Bronte-Stewart, B., Larson, N. and Keys, M. H.: Lessons from Serum Cholesterol Studies in Japan, Hawaii and Los Angeles. Ann. Int. Med. **48**: 83 (Jan.), 1958.

Studies on the diet, the serum cholesterol, and the frequency of atherosclerosis and coronary heart disease have been made in Japanese in Japan, where coronary heart disease is rare, in Hawaii, where it is fairly common but less so than among Caucasians, and in California, where the local Japanese are similar to the local Caucasians in regard to the frequency of the disease. In middle age, coronary heart disease is at least 10 times as common in the United States as in Japan. In 475 Japanese the serum cholesterol concentration showed a linear relationship to the percentage of calories provided by fats in the diet from a low, among farmers at Koga and a slightly higher average among miners at Shime, Japan, to a high among Nisei in Los Angeles, who were not significantly different from local Caucasians in this respect. These differences (averaging 96 mg. per 100 ml. comparing 40- to 49-year-old Koga farmers, eating less than 10 per cent fat calories, with Los Angeles Nisei of the same age, eating

39 per cent fat calories) were accounted for by beta lipoprotein cholesterol, the alpha fraction showing no significant variation. These differences are not accounted for by the differences in climate, relative obesity, physical activity, the use of alcohol and tobacco, the concentration of protein in the diet, or the intake of "essential" fatty acids. The findings on the Japanese are consistent with the theory that an important factor in producing differences in the frequency of coronary heart disease in populations is the proportion of calories in the diet provided by fats, particularly the common saturated fats.

WENDKOS

Deming, Q. B., Mosback, E. H., Bevans, M., Daly, M. M., Abell, L. L., Martin, E., Brun, L. M., Halpern, E., and Kaplan, R.: Blood Pressure, Cholesterol Content of Serum and Tissues, and Atherogenesis in the Rat. The Effect of Variations in Blood Pressure on the Cholesterol Content of Serum and Tissues and on the Development of Atherosclerosis in Rats on a High Cholesterol Diet. J. Exper. Med. **107**: 581 (April), 1958.

Data are presented indicating that in rats the presence of hypertension, whether induced by desoxycorticosterone and salt or by compression of 1 renal artery and removal of the other kidney, results in a greater degree of hypercholesterolemia and hyperlipemia than is found in normotensive rats maintained on the same "atherogenic diet" for the same period of time. The induction of hypertension by desoxycorticosterone and salt was found to accelerate the development of hypercholesterolemia, hyperlipemia, increase in tissue cholesterol content, and atherosclerotic changes in the intima, but desoxycorticosterone without salt or salt without desoxycorticosterone did not produce these effects. There was a positive correlation between the extent of the atherosclerotic lesions and the serum cholesterol concentration and also between blood pressure and the degree of hypercholesterolemia. It is uncertain as to whether the increase in atherosclerosis in the hypertensive animals is dependent on the increased lipid content of serum and tissues or on a local effect of the elevated blood pressure.

SAGALL

Leupold, F.: Serum Lipids and Serum Iodine Number in Normal Persons and Patients with Arteriosclerosis. Ztschr. Kreislaufforsch. **47**: 281 (April), 1958.

The serum iodine number (iodine capacity of serum lipids in mg. of iodine per 100 ml. of serum) had an average value of 705 in 100 normal persons while in 20 patients with arteriosclerosis the average was 1,087; the differences in other serum lipids were far less significant. Oral medication with unsaturated fatty acids and a surface-active substance of the "Tween" type in normal persons led to fluctuations of the serum lipids exceeding those appearing spontaneously. In several persons with arteriosclerosis this medication caused a decrease of the serum iodine number and cholesterol especially in its ester form, but no definite change in serum phosphatides.

LEPESCHKIN

BLOOD COAGULATION AND THROMBOEMBOLISM

Beckwith, R., Huffman, E. R., Eiseman, B., and Blount, S. G., Jr.: Chronic Aortoiliac Thrombosis. A Review of Sixty-five Cases. New England J. Med. **258**: 721 (April 10), 1958.

The records of sixty-five patients with chronic aortoiliac thrombosis encountered from 1951 to 1956 were reviewed. The diagnosis in each patient was confirmed by translumbar aortography, autopsy, or operation. In this series 48 per cent were less than 60 years of age, 23 per cent less than 50, and 6 per cent less than 40 years of age. Intermittent claudication involving both the leg and the hip area was considered characteristic of chronic aortoiliac thrombosis. In 32 of the 65 patients a phase of accelerated progression of symptoms was encountered and attributed to extension of the aortoiliac thrombosis or occlusive disease involving the collateral vessels, or both. Decreased sexual potency was found in 23 patients. Trophic changes, decreased or absent hair growth, and lowered skin temperature in the lower extremities were frequently observed. The absence of femoral artery pulsation was the greatest single important physical finding. Aortography, performed whenever possible, was of value in confirming the diagnosis and in demonstrating the location and extent of the occlusive process, but failed to give information of the degree of arteriosclerosis peripheral to the aortoiliac thrombosis and also underestimated the actual extent of the thrombotic process as determined by surgical exploration or pathologic evaluation. In 86 per cent of these patients significant cardiac, renal, hypertensive or cerebrovascular disease was found, indicating that chronic aortoiliac thrombosis is but one manifestation of a generalized process, atherosclerosis. Because of this a thorough evaluation of the entire cardiovascular system should be performed on such patients before any surgical intervention is attempted for chronic aortoiliac thrombosis.

SAGALL

CONGENITAL ANOMALIES

Mar[illegible]ell, G. M., Rowe, G. G., and Crumpton, C. W. A Clinical and Haemodynamic Study of Ventricular Septal Defect in Infants. Arch. Dis. Childhood **33**: 67 (Feb.), 1958.

The authors review the clinical features, symptomatology, physical signs, and studies of cardiac catheterization in 16 patients with ventricular septal defect occurring in infants, aged 1 year or less. The commonest symptoms were failure of growth, refusal to take food, and frequent respiratory infections. The most remarkable sign according to the authors was failure in growth. The physical examination usually revealed a palpable thrill in the systolic region over the left lower interspaces, a split second sound, and an iron deficiency anemia. The x-ray studies showed cardiac enlargement. Most of the patients showed a right bundle-branch block in the electrocardiogram. All the patients were catheterized and the pressures in the right atria and great veins were normal. Right ventricular hypertension occurred in all. Pulmonary hypertension occurred in all of the individuals save for 1. There was significant oxygen unsaturation in 7 of the 16 patients. The left-to-right shunt was less in this group as compared with older children, and it was thought this was so because of the high incidence of right ventricular hypertension. When figuring out the work index, it became obvious that the work of the right ventricle was greatly increased over adult standards. The authors stress the fact that the problem in this age group is not one of the shunt, but of the resultant or coincident pulmonary hypertension. The rise in right ventricular work load in the majority of these patients explains the high instance of right-sided failure in this series. Growth failure is quite severe. For these reasons the authors point out that simple ventricular septal defect is not the benign disease that it formerly was thought to be.

HARVEY

Mos[illegible], A. J., Adams, F. H., Latta, H., O'Loughlin, B. J., and Longmire, W. P., Jr.: Congenital Stenosis of the Aortic and Pulmonary Valvular Areas of the Heart. Indications for Early Surgical Relief. J. Dis. Child. **95**: 46 (Jan.), 1958.

This report stresses the grave prognostic import of congestive heart failure in infants with isolated pulmonic stenosis, or aortic or subaortic stenosis. Three case reports are presented of infants under the age of 2 in whom there was clinical evidence of either pulmonic or aortic valvular stenosis as isolated lesions. All 3 of the children developed heart failure and although operation was performed on all 3, 2 died—not, it is felt, as a result of the operation, but because the congestive heart failure and strain were more than the organism could bear. Clinical recognition of this lesion is difficult. Some of the diagnostic features include a loud, harsh systolic murmur, maximal in the second interspace to the left of the sternum with pulmonic stenosis and to the right of the sternum with aortic or sub-aortic stenosis. A thrill may accompany the murmur. Cyanosis may appear, particularly when heart failure results. X-ray will reveal evidence of appropriate chamber enlargement, depending upon which valve is involved. Milder forms of such stenoses are difficult to diagnose clinically, but right heart catheterization may be indicated. Indications for surgery are not clearly delineated as yet, but it is the feeling of this group that in any child with this lesion and a history of syncope, or exercise intolerance, or pronounced cardiac enlargement, surgery should be performed. promptly. Following these principles 2 patients with this lesion were subjected to early operation. It is believed that both children were afforded relief where otherwise death might have resulted.

HARVEY

Griffin, J. F. and Koman, G. M.: Severe Aortic Insufficiency in Marfan's Syndrome. Ann. Int. Med. **48**: 174 (Jan.), 1958.

A necropsied case of Marfan's syndrome is presented. The patient, 37-year-old white woman, died from left ventricular insufficiency as a consequence of severe aortic regurgitation. She had most of the classical clinical manifestations of the Marfan's syndrome, including arachnodactyly, myopia with a history of subluxation of the lens, a deficiency of subcutaneous fat, a high-arched palate, large ears, and prominent supraorbital ridges. In addition she presented a prominent infundibular thoracic deformity. Auscultation constantly demonstrated aortic regurgitation with an enlarged heart. The necropsy revealed a fusiform dilatation 10 cm. in length in the ascending aorta. This produced a relaxation of the aortic annulus with resulting valvular insufficiency. The microscopic changes in the aortic wall consisted of widening and fibrillation of the internal elastic membrane; the elastic fibers in the media of the affected aorta were broad and frayed and were considerably separated from each other. The result of this wide spacing of the parallel running elastic fibers was a separation by small cystic spaces of the muscle fibers of the media. In the medical literature, there are more than 50 case reports of necropsied examples of the Marfan's syndrome. In 80 per cent of these cases, medionecrosis cystica in the wall of the aorta or

of the pulmonary artery was present. Aneurysmal dilatation of the ascending aorta was found in 66 per cent. Dissecting aneurysm in the aorta occurred in about 30 per cent of the cases. The syndrome is a hereditary one, and is one of the less common causes of aortic insufficiency.

WENDKOS

CONGESTIVE HEART FAILURE

Aravanis, C. and Luisada, A. A.: Clinical Comparison of Six Digitalis Preparations by the Parenteral Route. Am. J. Cardiol. **1**: 706 (June), 1958.

Each of 6 groups of 21 elderly patients in congestive heart failure was digitalized and maintained on a different digitalis preparation, usually given intravenously. The response was studied by simple clinical means over a period of 1 week. Oubain, then digitoxin were the most rapid acting. Digitoxin, acetyldigitoxin, and digoxin had the greatest decongestant effect and also led to the most marked reduction in heart size. Heart rate slowing was the most pronounced after desacetyllanatoside C and digoxin, while the latter was the more toxic. Acetyl-digitoxin and digitoxin were the best drugs over-all, the latter being possibly inferior inasmuch as it caused the most marked electrocardiographic changes. Gitalin in general placed intermediately.

ROGERS

CORONARY ARTERY DISEASE

Pollack, A. A.: Insurability After a Coronary Occlusion. New York State J. Med. **57**: 3331 (Oct. 15), 1957.

Life insurance has become available in recent years to those patients who have sustained 1 attack of acute coronary occlusion with myocardial infarction. In order to qualify for this protection, the applicant must be working full time; he must not have been disabled for over 6 months at the time of his attack, which must have occurred at least 1 year previously. In addition, his present weight and blood pressure must be normal for the corresponding age and body build, and he must have no symptoms of coronary insufficiency. His electrocardiogram does not necessarily have to be normal, but it must be stable for at least the year prior to application for insurance. Other factors leading to disqualification are peripheral vascular disease, gout, eyeground changes of atherosclerosis, renal disease, diabetes, or a history of congestive heart failure. The premium is rated on the basis of the available data for life expectancy for these patients as compared with the normal life expectancy. Mortality rates for individuals who have sustained a myocardial infarction are particularly high in the young (30 to 39 years) group, but decrease with the duration of the survival time in all groups. Only the most favorable of the patients who have sustained an acute coronary occlusion are now insurable, but as knowledge and experience with this type of impairment increase, more liberal underwriting should become available.

KRAUS

Hilleboe, H. E.: Some Epidemiologic Aspects of Coronary Artery Disease. J. Chron. Dis. **6**: 210 (Sept.), 1957.

In his discussion, the author has drawn on the views expressed by the study group of the World Health Organization which met in Geneva, Switzerland, in November 1955 to consider this problem. At this meeting it was concluded that there was no clear-cut scientific evidence to show that any particular factor causes or contributes measurably to the development of coronary artery disease. From his own observations, the author makes the following assumptions with the suggestion that they be used to form hypotheses for field testing. 1. Liberal caloric intake and fat in the diet appear to be associated with increased blood lipid levels in human beings under varying modes of life. 2. Human diets with unrestricted fats, especially some of the saturated fatty acids, appear to be associated with coronary atherosclerosis, particularly in adult males but this is not a causal relationship. 3. Blood lipids, especially cholesterol beta lipoprotein fractions, appear to be higher in groups of persons with myocardial damage compared to normal persons, although the range of values found shows considerable variation and overlap in both groups. 4. Adult females, prior to menopause, are not affected with coronary atherosclerosis nearly as much as males, nor do they have anywhere near as much myocardial damage. 5. Other factors, especially blood coagulation, constitution, overweight, hormones, physical exercise, and mental stress, appear to have significant roles in the development of both coronary atherosclerosis and myocardial damage.

MAXWELL

Paton, B. C.: The Accuracy of Diagnosis of Myocardial Infarction. A Clinicopathologic Study. Am. J. Med. **23**: 761 (Nov.), 1957.

Two hundred sixty-six postmortem records were reviewed of patients found to have died from myocardial infarction or suspected of dying from this cause. They were divided into (a) cases where the clinical diagnosis was confirmed, (b) cases where the clinical diagnosis was not e-

firmed and (c) cases where unsuspected myocardial infarcts were found. The accuracy rate of the diagnosis of myocardial infarction was only 4 per cent. The major diagnostic errors occurred in patients who died suddenly or presented atypical symptoms. Patients with coronary atheroma but without infarction, those with pulmonary emboli, and postoperative cases were responsible for most errors in the second group. The cases of the third group often presented as congestive heart failure of unknown etiology or were thought to have had pulmonary emboli. Correct electrocardiographic interpretation was made in 91 of 97 cases in which a recent electrocardiogram was taken. Three of the other 6 had left bundle-branch block and the other 3 had nonspecific changes. About 50 per cent of sudden deaths are due to myocardial infarction. Anyone with a previous evidence of coronary artery disease who died suddenly is almost certain to have died of myocardial infarction.

KURLAND

Nichol, E. S., Keyes, J. N., Borg, J. F., Coogan, T. J., Boehrer, J. J., Mullins, W. L., Scott, T., Page, R., Griffith, G. C., and Massie, E.: Long-Term Anticoagulant Therapy in Coronary Atherosclerosis. Am. Heart J. 55: 142 (Jan.), 1958.

A compilation of the results of the pooled clinical investigation of 1091 patients with coronary atherosclerosis treated with long-term anticoagulants by a number of widely separated clinicians is presented. The duration of treatment varied from 3 to as long as 100 months with an average duration of therapy of 22.4 months. Of this group 4.2 per cent developed non-fatal thromboembolism and 12.0 per cent (131 patients) died while on the regimen, mostly from cardiac disease. Hemorrhage of significant character occurred at some time during treatment in 220 patients (20.1 per cent), but in only 6 could hemorrhagic complications be incriminated as causing death. Three hundred and nineteen patients abandoned the anticoagulant regime for 1 reason or another. Follow-up studies of these showed that 28.2 per cent died within 4 years, chiefly due to cardiac disease. An additional 417 patients not given anticoagulants were also used as "controls." Of this group during the follow-up period 37.4 per cent died, the majority from cardiovascular disease. The authors believe that the data of this study although not amenable to statistical analysis because of the many variables warrant the conclusion that the continuing administration of anticoagulants does prevent recurrent attacks of myocardial infarctions.

SAGALL

Littler, T. R., and McKendrick, C. S.: L-Noradrenaline in Myocardial Infarction. Lancet 2: 825 (Oct. 26), 1957.

Experimental and clinical studies are presented that demonstrate the tendency of norepinephrine to produce cardiac arrhythmias. When 0.5 μg. per Kg. was administered to monkeys and dogs under pentobarbital and ether anesthesia, ventricular extrasystoles resulted. In larger doses, nodal rhythm, transient atrioventricular dissociation, multifocal ventricular extrasystoles, and paroxysms of ventricular tachycardia were observed. These arrhythmias were prevented by premedication with large doses of atropine. Two cases are presented in which the infusion of norepinephrine for shock from myocardial infarction was associated with ventricular arrhythmias. The total experience with norepinephrine in 22 severely shocked patients with myocardial infarction was disappointing. Pressor response was noted in 10; none survived.

KURLAND

LaDue, J. S.: Laboratory Aids in Diagnosis of Myocardial Infarction. J.A.M.A. 165: 1776 (Dec. 7), 1957.

The significance of certain enzymes in the serum (glutamic oxalacetic transaminase (SGO-T) glutamic pyruvic transaminase (SGP-T), and lactic dehydrogenase (SLD), was demonstrated by the experimental production of myocardial infarction and ischemia in dogs. Of these enzymes the SGO-T concentration is probably the most useful in diagnosis of human myocardial infarction, and within 48 hours in such cases will rise from 1.5 to 20 times the normal figure. This increased level of SGO-T lasts only 4-5 days; however, the SLD may remain elevated 2-3 days longer than the other 2 enzyme levels. When SGO-T activity is elevated, acute myocardial damage must be presumed to be present in the absence of known active liver disease. The nonspecific phase-reactants, erythrocyte sedimentation rates, C-reactive protein and plasma fibrinogen levels are also discussed. All these nonspecific phase reactant tests may be positive in infectious diseases as mild as an upper respiratory infection, in gastrointestinal diseases, acute gout, and in neoplastic diseases and sometimes with severe congestive heart failure. They will of course be positive in pulmonary infarction, pericarditis, acute rheumatic fever, rheumatoid arthritis and other collagen diseases. The test for CRP remains positive for as long as 3 to 7 weeks so that where blood samples are not obtained with the first 4 days following myocardial infarction this test would be of particular value as the SGO-T reading may be normal after the fourth day. The

nonspecific phase-reactant tests when positive must be carefully evaluated in the light of their nonspecificity. The behavior of the serum enzymes, SGO-T, SGP-T, and SLD, in the absence of active liver disease is valuable in confirming the diagnosis of acute myocardial infarction.

KITCHELL

Manchester, B.: The Prevention of Myocardial Infarction. Arch. Int. Med. 100: 959 (Dec.), 1957.

This report covers 712 patients with 1 or more myocardial infarctions carefully confirmed clinically and by electrocardiogram. A control group in which a placebo (ascorbic acid) was used and an untreated group were compared with a group receiving anticoagulants. Therapy other than anticoagulants and placebos was otherwise equivalent in all groups. For final evaluation there were 204 in the treated group, 200 in the control group, and 157 in the untreated group. The author claims that therapy with anticoagulants is practical, feasible, and economical by the use of a simple capillary blood prothrombin test. He reports a bleeding incidence of 2.9 per cent and this danger, he asserts, is far less than the inherent hazard of subsequent myocardial infarction. It is mandatory that the patient be cooperative and the physician be meticulous in the proper use of anticoagulants. The incidence of subsequent myocardial infarction was 3 times greater in the control and untreated group; the mortality rate was 8 times more in the control and untreated group than in the group treated with anticoagulants. Hence, when anticoagulants are correctly and adequately used, they will lower the incidence of subsequent myocardial infarction and mortality rates.

KRAUSE

Vineberg, A., and Walker, J.: Six Months to Six Years' Experience with Coronary Artery Insufficiency Treated by Internal Mammary Artery Implantation. Am. Heart J. 54: 851 (Dec.), 1957.

The results of surgical implantation of the internal mammary artery into the heart in 88 patients suffering from angina pectoris due to coronary artery disease are reported. The overall operative mortality rate was 14.7 per cent, but for the 68 patients with no angina at rest it was only 5.8 per cent. Of the 68 patients with no angina at rest 72.1 per cent were totally disabled prior to operation. After internal mammary implantation 54 patients (79.4 per cent) of this group returned to work and 53 patients (77.8 per cent) were free of pain or had slight or less pain. Of the 20 patients suffering from angina decubitus, all had been disabled for a long time prior to operation. After operation 7 (35 per cent) had no pain, less or slight pain and 6 (30 per cent) returned to work. The result in patients who had suffered from the disease a long time were generally not satisfactory, presumably because so much destruction of heart muscle had already taken place that revascularization could not help. The best results were obtained in patients who had been suffering, on an average, for 33 months. Internal mammary implantation is indicated in patients with proved coronary artery disease with typical angina pectoris who have failed to improve within 1 to 2 years of medical treatment. Contraindications include left ventricular failure, active disease; coronary occlusion with infarction within the previous 6 months; the presence of associated disease such as essential hypertension and severe diabetes, and patients with asymptomatic coronary artery disease.

SAGALL

Bellman, S., and Frank, H. A.: Vascular Channels Established by Implantation of a Systemic Artery into the Myocardium. Ann. Surg. 147: 425 (April), 1958.

In 21 dogs the left internal mammary artery was implanted into the anterior wall of the left ventricle according to the technic of Vineberg. The preparations were studied at intervals of 2.5 to 9 months after implantation by microangiography following the injection of Schlesinger mass and by standard histologic methods. It was found that most implants remained patent (although showing intimal changes resembling arteriosclerosis), gave off several branches, and also formed communication with the coronary tree. The factors considered critical for patency and branching of the implant included freeing and protection of the implant artery in its course to the heart and firm fixation of the implant artery at the end of the myocardial tunnel. Most branches that arose within the myocardial tunnel and all branches from the extracardiac portion of the implant were unrelated to preformed gross openings in the artery. The development of branches was not influenced by variations in the stripping of the adventitia or by myocardial ischemia produced by coronary ligation at the time of implantation. Communication between implant and normal coronary tree were found to be established by fine vessels located within the myocardium near the tunnel, whereas communications to tied coronary branches were large, tortuous, located on the surface of the heart and seemed to arise in part by enlargement of the fine subepicardial vessels that normally connect major coronary branches in the dog. The authors in-

cluded that the sparseness of the branching and the quite consistent appearance of degenerative changes in the implant artery constitute the major limitations of this method as a source of increased arterial flow to the myocardium, but the large size of the connections formed, especially with dilated coronary arteries, warrants continuing study of the implantation principle.

SAGALL

Segal, R. L., Silver, S., Yohalem, S. B., and Newburger, R. A.: Use of Radioactive Iodine in the Treatment of Angina Pectoris. Am. J. Cardiol. 1: 771 (June), 1958.

Iodine^{131} therapy of intractable angina pectoris in 65 euthyroid patients was followed by improvement that was excellent in 15, good in 23, and nil or worse in 27. The likelihood of anginal relief did not appear to be greatly influenced by the presence of hypertension, old myocardial infarction, congestive heart failure, tachycardia, diabetes mellitus, hypercholesterolemia, intermittent claudication, or angina decubitus, although all 8 deaths occurred in the latter group. Three or more of these deaths may have been precipitated by radiation thyroiditis, a complication that can be minimized by administering the I^{131} in 2 or 3 divided doses. These results are comparable to those of most other physicians, and the authors concluded that this treatment is useful in a select small number of anginal patients.

ROGERS

Toledo, A. N., de Carvalho, A. A., Dohmann, H., Roubach, R., Zaniolo, W., and Azevedo, A. C.: The Electrocardiogram in Mitral Stenosis. Arq. brasil. de cardiol. **9**: 215 (Dec.), 1956.

A study is presented of the electrocardiogram in 58 patients with pure or predominant mitral stenosis. The electrocardiographic findings are correlated with clinical, radiologic, and hemodynamic data. Atrial fibrillation has been found in 22.5 per cent of these patients; the average age of this subgroup was 36 years, while it was 27.5 in the nonfibrillators; the mean right ventricular pressure among the fibrillators was 73.8 mm. Hg; all but 2 had a large left atrium; only 36 per cent were definitely improved by commissurotomy. A "mitral" configuration of the P wave was noted in 3 per cent of the patients in sinus rhythm; in 73 per cent of those having an enlarged P wave (0.1 second or more), the left atrium was not enlarged or only moderately so. The direction of the mean axis of the P wave (in the frontal plane) could not be associated with other findings of mitral disease; the height of the P wave was not correlated with right atrial enlargement. Right axis deviation of mean QRS (in the frontal plane) was associated with other signs of right ventricular hypertrophy in 84 per cent of the patients; only 3.5 per cent of those having an axis of less than 90° showed right ventricular hypertrophy. The relation $R/R+S=0.5$ in V_{3R} or V_E is a good index of right ventricular hypertrophy. The index $R\ V_1+S\ V_5>10.5$, a qR pattern in the right precordial leads, and a late "intrinsicoid" deflection (more than 0.03 second) are also good signs; the high voltage of the R wave in the precordial leads or in $_AV_R$, however, has not been a valid sign of right ventricular hypertrophy in this series. Incomplete right bundle-branch block was found also in patients with right ventricular systolic pressure lower than 50 mm. Hg; this pattern may appear in the postoperative period in patients who had shown right ventricular hypertrophy before surgery. Electrocardiographic evidence of right ventricular hypertrophy was found in 71 per cent of the patients with sinus rhythm and pulmonary hypertension and in 24 per cent of the fibrillators. The S-T segment and T-wave changes seen were primarily due to digitalis; a negative or flat T-wave in the left precordial leads had reverted to positive after commissurotomy.

CALABRESI

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Michel, D. Bockk, K., Hartleb, O., and Herbst, M.: Electrocardiogram and Heart Position. Arch. Kreislaufforsch. **26**: 112 (April), 1957.

A review of the literature makes it probable that anatomic rotation of the human heart does not exceed 45° about the sagittal axis and 25° about the longitudinal axis. A perfused frog heart was suspended in Ringer solution, with electrodes arranged in frontal and horizontal planes at a distance of twice the diameter of the heart. Rotation of the heart in the frontal plane caused a corresponding rotation of the QRS axis. Rotation about the longitudinal axis caused corresponding rotation in the horizontal plane when the heart was in the vertical position; it did not affect the frontal plane vectors if the heart was oriented for maximal amplitude of these vectors, but caused considerable shift when it was oriented for minimal amplitude. Rotation of the exposed dog heart about the sagital axis caused approximately the same rotation of the QRS vector in the frontal plane; rotation toward the right, which was accompanied by slight counterclockwise rotation about the longitudinal axis,

usually caused QR to appear in lead I. Rotation about the longitudinal axis influenced the frontal QRS vector only when the heart was rotated to the right in the frontal plane, and then only insignificantly; clockwise rotation sometimes caused appearance of a Q wave in lead III and disappearance of the Q wave in lead I, but these changes were very erratic. However, rotation, exceeding 30° usually changed the frontal plane QRS profoundly, especially when the QRS complex was of low voltage. Exposure of the heart caused no appreciable changes of the QRS complex in the frontal plane, so that these observations would be presumably valid also with a closed chest. It was concluded that the electrocardiographic criteria of clockwise or counterclockwise rotation of the heart have little relation to the anatomic heart position and are useful only as a description of certain electrocardiographic patterns.

LEPESCHKIN

Schweizer, W.: Electrocardiographic Observations in 300 Cardiac Catheterizations. Arch. Kreislaufforsch. **26**: 1 (April), 1957.

Extrasystoles appeared in 70 per cent of the catheterizations. Ventricular extrasystoles were most common; they appeared usually when the catheter was in the right ventricle and especially when it penetrated the atrioventricular (A-V) ring or when blood samples were taken. When they appeared with the catheter in the right atrium, they could not have been due to mechanical irritation of ventricular muscle. A Wolff-Parkinson-White pattern appeared once under these circumstances. A-V nodal extrasystoles were most common when the catheter was in the right ventricle, while atrial extrasystoles were most common when it was in the atrium. Slight changes in the QRS complex, sometimes appearing as alternans, were found in 17 per cent, right bundle-branch block in 8 per cent, left bundle-branch block in 3 per cent, wandering pacemaker in 10 per cent, atrial flutter in one per cent, and A-V block in 2 per cent. Supraventricular paroxymal tachycardia occurred in only 1 person. In 3 per cent transient elevation of the T wave or S-T segment was observed, especially in patients with pulmonary stenosis. Absence of all changes was seen in only 24 per cent, especially in women, in old persons, in small hearts, and in the presence of a slow heart rate. Most atrial disturbances appeared in the presence of elevated atrial pressure. In large hearts left bundle-branch block and escape beats were more common, right bundle-branch block and paroxysmal tachycardia less common. No relation of incidence was found to digitalization or to the size of the catheter.

LEPESCHKIN

Braunwald, E., Tanenbaum, H. L., and Morrow, A. G.: Localization of Left-to-Right Cardiac Shunts by Dye-Dilution Curves Following Injection into the Left Side of the Heart and into the Aorta. Am. J. Med. **24**: 203 (Feb.), 1958.

The localization of cardiac shunts by classic right heart catheterization is subject to error because of incomplete mixing of caval and right atrial blood, incomplete mixing of shunted and nonshunted blood, and variations in the physiologic state during sampling. Left heart and central aorta catheterization permits the injection of indicator substances in these areas. The resulting dilution curves recorded from a peripheral artery or a heat-flushed ear permit precise localization of left-to-right shunts. Without shunts the curve consists of a steep ascent and a smooth descent. When dye is injected proximal to a left-right-shunt the descent is interrupted by dye shunted through the pulmonary circulation. Injection distal to the shunt results in normal curves. Application in 80 cases has been helpful and without hazard.

KURLAND

Castellanos, A., Jr., Cano, L. A., and Calvino, J. M.: Post-Extrasystolic Changes in Rhythmicity and Conductivity During Established A-V Nodal Tachycardia. Cardiologia **32**: 212 (April), 1958.

Four electrocardiograms are illustrated revealing various influences of premature beats upon the mechanisms operating in accelerated atrioventricular nodal rhythms. The analysis was facilitated by recording esophageal leads that permitted precise determinations in the post-extrasystolic beats of P-R and R-P intervals, not evident in the standard leads. These clinical records are in keeping with observations of others in experimental atrioventricular nodal rhythms.

PICK

Rijlant, P.: Normal and Abnormal Vectorial Electrocardiograms and Vectorcardiograms in Man. Acta cardiol. **13**: 10 (Fasc. 1), 1958.

The author applied the results of previous experimental investigations to a study of the distribution of electromotive forces in the human torso in 500 normal and abnormal individuals. In addition to the simultaneous recording of frontal, horizontal, and sagittal vectorcardiograms and vertical, transverse, and anteroposterior bipolar electrocardiograms, vectorcardiograms were recorded in 3 arbitrarily chosen orthogonal planes. These planes are defined by 3 angular deflections in relation to the vertical and horizontal axis of the body. Bipolar electrocardiograms were obtained in the same planes synchronously. Statistical evaluation of the data revealed,

that f the 500 individuals examined, the electric event in the heart were limited to a flat surface normal subjects as well as one in most pathol gic cases. The characteristics of this surfa are represented by 2 orthogonal electrocardi rams: lead Y, which contains the largest vecto and X, the perpendicular component. Only minim l electric activity was demonstrable for the Z omponent, at a right angle to the surface. In a mall number of normal and abnormal subjects, lectric activity took place in 2 or 3 planes, usual at right angles to each other. The authors concl sions are that in the majority of individua s, in the absence or presence of cardiac pathology, there is always a high degree of bilateral symmetry in the electrogenesis of the heart.

PICK

Duboudoz, P.: Ventricular Electrogenesis in the Light of New Experimental Facts. Cardiologia 32: 193 (April), 1958.

Recent advances in the electrophysiology of the heart are reviewed. Studies of transmembrane and intramural potentials and investigations of the spread of the excitation wave through the ventricular wall permit an acceptable explanation of the genesis of the QRS deflections, based on pure physical principles. The intrinsicoid deflection can be considered to represent the passage of a polarized layer close to the electrode. The resulting electrocardiographic pattern depends on the position of the electrode. An intramural electrode records a rapid negative downstroke, whereas an epicardial electrode gives diphasic deflections. These differences are attributable to the relation of a flat polarized surface to the global shape of the ventricles. The distribution of potential variations within the ventricular walls as determined by multiple intramural electrodes at various depths is in keeping with Durrer's hypothesis of rapid spread of the excitation wave in the inner shell of the ventricular wall by way of the Purkinje system.

PICK

Pick, A., and Fisch, C.: Ventricular Pre-Excitation (WPW) in the Presence of Bundle Branch Block. Am. Heart J. 55: 504 (April), 1958.

Three cases are reported showing the rare combination of ventricular pre-excitation with a right or left bundle-branch block. One of the 2 cases of left bundle-branch block was also further complicated by a co-existent first degree atrioventricular block. The variety of electrocardiographic manifestations that may result from the combination of these 2 types of abnormal ventricular activation is discussed in the light of present knowledge concerning impulse propagation under normal and anomalous circumstances.

SAGALL

Sekelj, P., Jegier, W., and Johnson, A. L.: Automatic Electronic Computer for the Estimation of Arterial Concentration of Evans Blue Dye. Am. Heart J. 55: 485 (April), 1958.

The authors describe an electronic automatic computing ear oximeter for the estimation of arterial concentration of Evans blue dye in an attempt to eliminate the technically difficult and tedious collection and analysis of calibrating samples in cardiac-output measurements. The sensitivity of the recording system was found to be adequate for recording several consecutive dye-dilution curves when small quantities of dye were used. In 81 comparison tests a close correlation was found between the results of the dye-concentration values computed automatically and those obtained by calculation in normal subjects and in patients with various cardiovascular anomalies. The results reported in this article and in others to be published separately in a paper on determination of cardiac output indicate that the method described allows quantitative estimation of the dye concentration in the circulating arterial blood.

SAGALL

Haroutunian, L. M., Neill, C. A., and Otis, A. B.: The Contour of the Right Atrial Wave in Twenty-Seven Cases of Atrial Septal Defect and in Other Cardiac Conditions. Bull. Johns Hopkins Hosp. 102: 176 (April), 1958.

The contours of the venous A, C, and V waves were studied in various cardiac conditions by means of cardiac catheterization. A brief history of the descriptions of A, C, and V venous waves is given. Twenty-seven cases of atrial septal defect of the secundum type were studied; it was found that the characteristic pattern of the A-C-V waves was an M-shaped curve. This pattern was compared with the pattern in normal subjects and in patients with anomalous pulmonary venous drainage, constrictive pericarditis, myxomas of the right and left atria, and individuals who were suffering from various arrhythmias. This M-shaped curve was not observed in any patients with these other cardiac conditions. The authors think this contour is due to the presence of the atrial defect, and they suggest that the major shunt through the defect occurs at the time of atrial filling, that is, the time of the V wave. This large V wave disappears when severe pulmonary hypertension supervenes and the shunt changes direction.

HARVEY

Gillmann, H.: Electrocardiographic Analysis by Means of Sector Diagrams in Different Degrees and Types of Pressure and Volume Overload of the Right Ventricle. Arch. Kreislaufforsch. 28: 79 (April), 1958.

In 140 patients with congenital heart disease the vector direction during P, T, and at 0.02, 0.04, 0.06 and 0.08 seconds after the beginning of QRS was determined from the synchronously registered standard limb and precordial leads, and subdivided into 12 sectors in the frontal plane and 4 sectors in the horizontal plane. In 60 patients with atrial septal defect the first QRS vector was situated considerably more to the right (100°) and the second vector more to the left (—60°) in the foramen primum than in the foramen secundum type (0° and 100° respectively); the third and fourth QRS vectors were similar in both groups (150° and —160° respectively). The P-R interval was also much longer in the "primum" group. In 30 patients with pulmonary stenosis and 20 with trilogy of Fallot the first 2 QRS vectors had the same direction as in atrial defects, but the second 2 vectors were deviated more to the right. The duration of QRS increased with right ventricular flow and showed little dependence on the pressure, but the incidence of complete right-bundle branch block showed no dependence on these factors. In persistent ductus (30 cases) the R vector showed wide scatter in the frontal plane. In all cases except those of trilogy, increase of right ventricular pressure was accompanied by a more clockwise rotation, of QRS vectors in both the frontal and the horizontal plane; in trilogy it was accompanied by a more counterclockwise rotation, probably because the increased shunt led to left ventricular overload. Deviation of the QRS vectors to the right and the T vectors to the left showed the best correlation to right ventricular pressure in pure pulmonary stenosis. The duration of P also seemed to correlate with the right ventricular pressure in all cases except those of trilogy.

LEPESCHKIN

Froment, R., Gallavardin, L., Aron, M. and Cahen, P.: Autonomous Form of Atrial Tachycardia with Atrioventricular Block Differing from Paroxysmal Tachycardia and Flutter. Arch. mal. coeur **51**: 156 (Feb.), 1958.

Five typical cases from a large series, described in detail in this article, were characterized by the permanent rather than paroxysmal character of their tachycardia, which may persist for 1 or 2 decades, appears on the basis of organic heart disease, and leads to progressive heart failure often terminating in atrial fibrillation. One patient showed at autopsy diffuse myocardial fibrosis, which included the atrium. The rate of the tachycardia oscillates around 200, but on certain occasions may fall as low as 120. It is usually accompanied by 2:1 or 3:2 atrioventricular block, which must depend on lesions of the atrioventricular node as it appears at relatively low heart rates. The P-wave axis is about +60° (—30 to +85). Multiple intracardiac leads in 1 patient showed that the upper right atrium was activated first, whereas the lower right atrium and the left atrium were activated last, with an interval of 0.14 second between them. This intraatrial conduction delay was similar to that found in flutter, but in distinction to the latter, the repolarization phase equaled or exceeded the depolarization phase, and there was no tendency to monodromic conduction. The direction of excitation also differed from that found in the common type of flutter.

LEPESCHKIN

Wick, E.: A Simple Method of Controlling the Respiratory Pressure During the Experiment of Valsalva. Ztschr. Kreislaufforsch. 47 304 (April), 1958.

Sudden changes of intrathoracic pressure during the Valsalva maneuver make it sometimes impossible to register intracardiac pressures at high sensitivity. This pressure can be held practically constant if an outlet with a spring valve is inserted between the mouthpiece and the manometer. The tension of the spring can be adjusted for any desired pressure.

LEPESCHKIN

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

McCue, C. M.: Myocarditis in Infancy. Pediatrics **21**: 710 (May), 1958.

Three cases of myocarditis occurring in infants below the age of 1 year are presented. Clinical manifestations include cardiac enlargement without murmur, electrocardiographic changes, particularly of the T wave and S-T segments, a normal blood pressure, and no evidence of rheumatic or congenital heart disease. Two of these children were recognized early and were treated with antibiotics and digitalis and this was thought to have changed the course of the disease and permitted the children to survive. A third child was recognized at 9 months of age as having a large heart, rapid pulse, and respiratory rate, but the diagnosis of myocarditis was not made until a month later when the child developed frank cardiac failure. Death followed in a few hours before digitalis could be administered. A complete pathologic report is given on this child, and the changes in the myocardium were shown to be very extensive. The author is of the opinion that the chemotherapy administered to the first 2 patients early in the course of their disease and its continuation for many months after the acute episode was extremely helpful in the treatment.

The author makes a plea for the clinical diagnosis of myocarditis to be made early in its course and stresses that this condition may occur in children less than 1 year of age who otherwise might be thought to have endocardial fibroelastosis.

HARVEY

HYPERTENSION

Moyer, J. H., Heider, C., Pevey, K., and Ford, R. V.: The Vascular Status of a Heterogeneous Group of Patients with Hypertension, with Particular Emphasis on Renal Function. Am. J. Med. **24**: 164 (Feb.), 1958.

The status of renal function was determined in 133 hypertensive patients by means of clearance tests, and the elevation of blood pressure was correlated with the incidence and severity of depressed renal function and the complications of hypertension in other areas. Not only was reduced renal function found in the hypertensive patients, but a correlation was noted between the severity of the hypertension based upon diastolic blood pressure elevation and the degree of decreased function. As diastolic pressure rose, the glomerular filtration rate and renal blood flow decreased. Similarly correlated was the incidence of complications in other areas, especially roentgen evidence of cardiomegaly, incidence of cerebrovascular accidents, grades 3 and 4 eyeground changes, and abnormal findings in the urine. Patients with malignant hypertension tended to have greater renal damage in association with more severe generalized vascular disease.

KURLAND

Gellman, D. D.: Reversible Hypertension and Unilateral Renal Artery Disease. Quart. J. Med. **27**: 103 (Jan.), 1958.

The degree of success achieved by unilateral nephrectomy in curing hypertension in man is difficult to estimate. The clinical equivalent of the "Goldblatt kidney" does, however, occasionally occur and previous reports of 26 patients are reviewed. The present paper draws attention to this important but rare condition, in which occlusion of the renal artery was a complication of occlusion of the abdominal aorta. A 65-year-old watchman suffering a rapid deterioration of vision was found to have severe hypertensive retinopathy. History revealed that for 3 years he had noted pain in the small of the back radiating to the buttocks and down the back of the thighs on walking 50 yards. Examination revealed pitting oedema, retinal hemorrhages, and a blood pressure of 220/115 mm. Hg. Pulsations in the femoral arteries were weak and delayed, but no pulsation could be felt in the posterior tibial or dorsalis pedis arteries. No pulsation could be felt over the abdominal aorta below the umbilicus, but a systolic murmur was heard over it. The superficial circumflex arteries were dilated. There were albumin, red cells and casts in the urine. An intravenous pyelogram revealed no excretion on the left side. An abdominal aortogram showed the aorta completely obstructed below the level of the first lumbar vertebra with occlusion of the left renal artery. Left nephrectomy was performed. Within 24 hours, the blood pressure fell and subsequently averaged 140/80 mm. Hg with subsidence of retinal and urinary findings. The condition should be suspected in patients with no family history who suffer rapidly progressive hypertensive disease. A history of unexplained abdominal pain is significant. Abdominal aortography is the most important investigation. Nephrectomy should be undertaken only if function of the remaining kidney is normal.

KURLAND

Widimsky, J., Fejfarová, H. M., Fejvar, Z., Dejdar, R., Exnerová, M. and Pirk, F.: Juvenile Hypertension. Arch. Kreislaufforsch. **28**: 100 (April), 1958.

Ninety-six patients 14 to 29 years old, who showed a blood pressure of 170/100 mm. Hg or more were subjected to detailed study. These persons showed symptoms of neurocirculatory imbalance more commonly than older patients with hypertension. Seventy per cent had accelerated circulation time and increased cardiac output and heart index, with normal peripheral resistance. Physical or mental work usually caused a further long-lasting increase of the output. The hypertension was usually labile during puberty but fixed in 45 per cent of the young adults. Hypertensive vascular changes in the ocular fundus were found in 25 per cent while cardiac hypertrophy was disclosed by fluoroscopy in 39 per cent. Electrocardiographic signs of left ventricular hypertrophy were found in 54 per cent of the younger and 61 per cent of the older group; they were 3 times more common in fixed than in labile hypertension. The conclusion is made that hypertension of long duration in young persons most commonly represents the initial phase of essential hypertension caused by elevation of the heart output.

LEPESCHKIN

McKendrick, C. S., and Jones, P. O.: Pentacynium Bis-Methylsulphate (Presidal) in the Management of Hypertension. Lancet **1**: 340 (Feb. 15), 1958.

Pentacynium, a new ganglionic-blocking agent, was given orally and parenterally to 30 severely hypertensive patients for 3 to 18 months. Follow-

ing a subcutaneous test dose, all patients but 1 showed a significant fall in blood pressure with the usual postural accentuation. The effective oral dose was 10 to 20 times the subcutaneous dose. Twenty-four of 30 patients showed satisfactory oral responses. Parenterally, it was equipotent with chlorisondamine and mecamylamine and 2 to 3 times as potent as pentolinium. Orally it was equipotent with chlorisondamine, twice the potency of pentolinium, and one-tenth as potent as mecamylamine. Cross-tolerance with other ganglionic-blocking agents was not evident. Reserpine increased the hypotensive effect by 10 to 20 mm. Hg. As with similar drugs, the side effects are due mainly to the associated parasympathetic blockage. These were similar to those of the other ganglionic-blocking substances but constipation was less severe. Consequently, as always, success depended more on the doctor's management of the patient than on the use of any individual drug.

KURLAND

Moyer, J. H., Heider, C., Pevey, K., and Ford, R. V.: The Effect of Treatment on the Vascular Deterioration Associated with Hypertension, with Particular Emphasis on Renal Function. Am. J. Med. **24**: 177 (Feb.), 1958.

This report compares the control and follow-up renal functional status in 45 patients with hypertension before and after adequate treatment with a group of 19 patients in whom hypertension was not treated. There was no difference in vascular deterioration between treated and untreated patients with mild to moderate elevation in blood pressure. In the treated patients with severe hypertension, there was no change in renal function before and after treatment although the mean blood pressure was reduced from 173 to 122 mm. Hg. The untreated patients in this group showed a marked reduction in function over a follow-up period of only 24 months. The blood urea nitrogen rose; the glomerular filtration rate and renal blood flow decreased. Treated patients in both groups showed a significant improvement in electrocardiographic changes and decrease in size of the heart by x-ray. In both treated and untreated patients mortality increased and prognosis became worse as glomerular filtration rate decreased. However, untreated patients showed a much higher mortality than treated patients in each group. Five patients died of cerebrovascular accidents within an average of 3 months of discontinuing treatment, suggesting a "rebound" rise in blood pressure. Twenty-one patients with malignant hypertension were treated. Only 2 of the 12 treated patients have died; all 9 of the untreated patients have died. Five patients with unilateral renal thrombosis and hypertension were studied. Glomerular filtration rate and renal blood flow were reduced in the contralateral kidney. As therapy was instituted and the blood pressure was reduced, renal function improved progressively in the unoccluded kidney.

KURLAND

PHARMACOLOGY

Quimby, C. W., Jr., Aviado, D. M., Jr., and Schmidt, C. F.: The Effects of Aminophylline and Other Xanthines on the Pulmonary Circulation. J. Pharmacol. and Exper. Ther. **122**: 396 (March), 1958.

Studies of the effects of aminophylline on the pulmonary and systemic circulation of the anesthetized dog revealed that an intravenous injection of 3 to 15 mg. per Kg. caused a fall in aortic blood pressure, usually a fall in pulmonary arterial blood pressure, stimulated the myocardial force of contraction, and increased pulmonary blood flow. Forty available xanthines were each dissolved in N/10 sodium hydroxide solution and injected in 5 to 50 mg. doses into the perfused lobar artery and femoral artery. All compounds tested revealed either dilatation for both the pulmonary and systemic circulation or constriction for both but never opposite effects, so that a truly selective pulmonary vasodilator was not found.

RINZLER

Moyer, J. H., Strawn, J. R., Kent, B. M., Seibert, R. and Handley, C. A.: Excretion Products of Meralluride (Mercuhydrin). Am. J. Cardiol. **1**: 601 (May), 1958.

Normal individuals and those with nonrefractory congestive heart failure receiving 2 ml. of meralluride excreted within 6 hours 60 to 70 per cent of the drug in virtually its administered form. Since there was a parallel elimination of sodium and of water, and since less than 5 per cent of the mercury was excreted in inorganic form, it appeared that meralluride itself was the active diuretic principle. In refractory heart failure, the administration of 2 ml. of meralluride was followed by an increase in inorganic mercurial excretion to as much as 21 per cent of the dose, which possibly was related to the prolonged retention of the meralluride. The value of the theophylline content of meralluride was shown by the finding of a lessened rate and quantity of organomercurial excretion in subjects receiving comparable amounts of meroxyl (meralluride less theophylline).

ROGERS

Gaffney, T. E., Kahn, J. B., Jr., Van Maanen, E. F., and Acheson, G. H.: A Mechanism of the Vagal Effect of Cardiac Glycosides. J. Pharmacol. & Exper. Therap. **122:** 423 (March), 1958.

The effects of vagal stimulation were studied in vagotomized, anesthetized dogs, in which blood pressure, respiration, and electrocardiograms were recorded and in open-chest preparations. Ouabain increased the sinus bradycardia produced by maximal vagal stimulation at frequencies of 15 per second or more, but not at 10 per second or lower. In the decentralized heart prepared by bilateral removal of the stellate ganglion and the sympathetic chains down to the fourth intercostal space, ouabain increased the atrioventricular block produced during rapid atrial stimulation at frequencies of 5 or 10 per second. In experiments on 3 heart-lung preparations ouabain was found to sensitize both the sinoatrial node and the atrioventricular node to acetylcholine.

RINZLER

PHYSIOLOGY

Berne, R. M., Jones, R. D., Cross, F. S.: Myocardial Hypothermia in Elective Cardiac Arrest. J. Appl. Physiol. **12:** 431 (May), 1958.

The surgical repair of congenital lesions of the human heart may be facilitated by the establishment of cardiac arrest or some means of coronary perfusion. This paper deals with a study of elective cardiac arrest produced by intracoronary injection of potassium citrate or acetylcholine in normothermic dogs and in dogs whose hearts were cooled to about 20 C. by infusion of cold blood into the coronary circulation. Arrest by potassium injection resulted in a high incidence of ventricular fibrillation and poor recovery. Acetylcholine injection produced cardiac arrest, which could not be maintained with or without cardiac hypothermia, and in 4 of 5 dogs, ventricular fibrillation occurred. Infusion of 100 to 200 ml. of cold blood into the coronary arteries after potassium arrest gave the lowest incidence of ventricular fibrillation and the best recoveries. However, coronary perfusion with cold blood alone, coronary perfusion with cold blood prior to potassium arrest, or potassium arrest followed by coronary perfusion with 100 to 200 ml. of warm blood showed a high incidence of ventricular fibrillation or postarrest recoveries, or both.

RINZLER

Brunwald, E., Fishman, A. P., Cournand, A.: Estimation of Volume of a Circulatory Model by the Hamilton and the Bradley Methods at Varying Flow Volume Ratios. J. Appl. Physiol. **2:** 445 (May), 1958.

Two methods for the measurement of the volume contained within a segment of the vascular bed under consideration were compared for accuracy in an artificial circulation model. These methods were the Hamilton mean circulation time and the Bradley equilibration. The Hamilton method is based on the principle that the volume contained in the vascular segment is equal to the rate of blood flow through the segment during the time interval required by an indicator to traverse the segment. Bradley's method is based on the principle of the volume of distribution of an indicator. The Hamilton method provided accurate volume measurements over the entire range of minute flow to volume ratios examined, that is, from 0.37 to 1.0 to 7.75 to 1.0. Accurate measurements with the Bradley method were possible only with minute flow to volume ratios below 4.0 to 1.0.

RINZLER

Roddie, I. C., and Shepherd, J. T.: Receptors in the High-Pressure and Low-Pressure Vascular Systems. Their Role in the Reflex Control of the Human Circulation. Lancet **1:** 493 (March 8), 1958.

The authors review results of recent experiments designed to elucidate in man the interrelationships between the high-pressure and low-pressure receptors with special reference to the control of vasomotor tone of the limbs. An example of receptors in a high-pressure system is seen when changes in carotid sinus pressure produce change in systemic blood pressure. Since there is no change in blood flow through the hand and forearm and no change in resistance to blood flow in the limbs, the changes must be due to changes in cardiac output or in resistance in other beds. An example of the role of receptors in a low-pressure system is seen when forearm blood flow increases consequent to passive elevation of the legs of a recumbent person. This vasodilatation is seen in the forearm but not the hand and is presumed to result from changes in muscle vessels probably by alteration of vasoconstrictive tone. These receptors in the low-pressure vascular system are important in the reflex regulation of the circulation in man, since by reflexly reducing resistance to blood flow through skeletal muscles, large increases in cardiac output can take place without a large rise in arterial pressure and cardiac work.

KURLAND

Karki, N. T.: The Effect of Changes in Ion Concentration on Ventricular Fibrillation Induced Electrically. J. Physiol. **141:** 366 (April), 1958.

A study is presented on the effect of electrolytes on fibrillation of the isolated perfused rabbit heart. An excised rabbit heart was perfused

in retrograde fashion through the aorta with normal Ringer's solution at body temperature. The electrolyte concentration could be varied. Fibrillation was induced electrically by stimulating at a high rate. It was found that if the concentrations of potassium, sodium, or chloride were reduced, fibrillation persisted once it had been initiated. It also persisted, once initiated, if there was a rise in the concentration of calcium. Adding magnesium to the perfusing fluid counteracted the effects of increased calcium concentration. There was an inverse relationship between calcium and potassium concentrations, for if calcium concentration was high as potassium concentration was reduced, fibrillation persistence increased.

HARVEY

Schubart, A. F., Marriott, H. J. L., and Gorten, R. J.: Isorhythmic Dissociation. Atrioventricular Dissociation with Synchronization. Am. J. Med. **24**: 209 (Feb.), 1958.

If 2 tissues with inherent pulsatility are placed in contact, although they lack anatomic continuity, there is a tendency for the 2 to assume synchronous rhythms. Five patients with atrioventricular dissociation are presented in which there was a tendency for atria and ventricles to contract almost synchronously. The following criteria for isorhythmic dissociation are presented. If for a few beats the dissociated atrial and ventricular pacemakers fall in step, synchronization may be suspected. If repeated periods of such synchronism are observed or if a disrupting influence such as a premature beat or Valsalva's maneuver is followed by a return to the synchronized relationship, the evidence is stronger. Best evidence is afforded by the observation that when the two impulses approximate, one pacemaker surrenders a feature of its identity such as an inherent arrhythmia.

KURLAND

Szekeres, L., Lichner, G. and Varga, F.: The Difference in Sensitivity of the Right and Left Ventricular Myocardium to Hypoxia. Arch. Kreislaufforsch. **28**: 125 (April), 1958.

In heart-lung preparations as well as in situ, hypoxia always caused a greater relative reduction in left ventricular pressure than in right ventricular pressure. The right ventricle continued to contract at a time when the left ventricle was practically at a standstill. These differences could not have been due to differences in the work done by the ventricles, as they were present also in isolated hearts perfused according to the method of Langendorff. They could be explained by the authors' observation that the oxygen consumption of minced left ventricular muscle in vitro was significantly greater than that of left ventricular muscle fibers, which makes oxygen diffusion into the center of the fiber more difficult.

LEPESCHKIN

Berglund, E., Borst, H. G., Duff, F., and Schreier, G. L.: Effect of Heart Rate on Cardiac Work, Myocardial Oxygen Consumption and Coronary Blood Flow in the Dog. Acta physiol. scandinav. **42**: 185 (April), 1958.

The effects of variations in heart rate on ventricular function, myocardial oxygen consumption, and coronary blood flow were studied in anesthetized, open-chest dogs. The heart rate was fixed at the desired rates by electric stimulation. When the heart rate was increased in steps from 33 to 80 beats per minute to 200 to 280 beats per minute, the cardiac output increased 0 to 73 per cent and reached a maximum at rates varying from 90 to 180 per minute. The stroke volume decreased progressively while aortic pressure rose slightly and pulse pressure was diminished. The myocardial oxygen consumption and left coronary flow increased. Ventricular function curves, that is, ventricular stroke work plotted against the respective mean atrial pressure, were always lower at the higher heart rates than at the lower. Myocardial oxygen consumption per unit of mechanical work was greater at the higher rates. Coronary blood flow per unit of work increased with rate. Coronary vascular resistance was always much lower at high heart rates than at low.

RINZLER

PULMONARY DISEASES

Fleischner, F. G.: Pulmonary Embolism. Canad. M.A.J. **78**: 653 (May), 1958.

The historic, pathogenetic, and diagnostic aspects of this important subject are presented along with illustrative case reports emphasizing roentgenologic findings. The frequent embolizations not resulting in infarction will likely present no diagnostic signs; but one should look for reduced aeration of the involved lung, diminished diaphragmatic excursion, and plate-like atelectasis. Infarction occurs usually in the lower lobes, and it is always contiguous to a pleural surface. The common cushion rather than triangular shape may be seen only after a fluoroscopic search. Chronic or subacute cases with pulmonary hypertension may show dilatation of the pulmonary arteries and increased contiguity of the heart shadow against the sternum, indicating right ventricular enlargement. The detection of pulmonary embolism will depend primarily on the thorough clinical evaluation of the individual having unexplained acute dyspn

and chest pain, utilizing roentgenologic, electrocardiographic, and vectorcardiographic technics for confirmation.

ROGERS

Schmitz, H. and Thurn, P.: On Asymmetry of the Pulmonary Arteries. Fortschr. Röntgenstr. **88**: 1 (Feb.), 1958.

Of 30 patients with unilateral pulmonary hypoplasia, 20 showed congenital atresia or stenosis of pulmonary artery associated with other congenital cardiac defects, and 2 showed this condition as an isolated finding. One patient showed acquired inflammatory pulmonary thrombosis, while 7 patients showed unilateral pulmonary emphysema with destruction of parenchyma as a result of chronic pulmonary disease. The main radiologic signs were increased transparency of the involved lung; in the case of hypoplasia both the central and the peripheral arteries were narrow while in chronic emphysema the peripheral arteries were narrow while the central arteries were normal or widened.

LEPESCHKIN

Cordeiro, R.: Pulmonary Atelectasis. Some Aspects of Its Hemodynamics, with Reference to Broncho-Pulmonary Arterial Anastomoses. Arch. mal. coeur **51**: 113 (Feb.), 1958.

In 7 patients with chronic unilateral pulmonary atelectasis the wedge pressure in the pulmonary artery of the atelectatic lung was greater than the pulmonary arterial pressure, and showed a systolic maximum. The pulmonary arterial oxygen saturation in this lung was elevated and approached that of systemic arterial blood. These peculiarities can be explained by arterial bronchopulmonary anastomoses, together with increased peripheral resistance in the atelectatic lung. It is possible that a systolic maximum in the pulmonary capillary pressure curve which was found in other patients in certain positions of the catheter may have been due to the presence of local bronchopulmonary arterial anastomoses.

LEPESCHKIN

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Pearse, A. G. E., and MacPherson, C. R.: Renal Histochemistry in Potassium Depletion. J. Path. Bact. **75**: 69 (Jan.), 1958.

The authors depleted young male hooded rats of potassium by placing them on a potassium-deficient diet, combined with a resin and sacrificing the animals after given periods of time on the diet and also after depletion. The kidneys were removed immediately upon sacrifice and bisected. Two of the half kidneys were fixed for routine histologic study and one-half kidney was fixed for enzyme and lipid study by frozen section while the other half kidney was studied immediately with fresh frozen sectioning, enabling the authors to study various enzymes in the slices. The authors found that potassium deficiency caused histologic changes in all zones of the kidney, except for the glomeruli and the intertubular capillaries. The authors found that the following enzyme systems were not affected by potassium depletion: alkaline phosphatase, acid phosphatase, nonspecific esterases, succinic dehydrogenase. DPN-di-phosphorylase and TPN-di-phosphorylase were diminished in the potassium-deficient kidneys. The results of these broad-spectrum histochemical tests in the potassium-depleted animals suggest to the authors that potassium deficiency effects protein metabolism and the permeability of the tubular cells to proteins and metabolites and the processes of cell respiration and oxidative phosphorylation.

HARVEY

ROENTGENOLOGY

Bogsch, A.: Contributions to the Roentgenological Delineation of the Pulmonary Artery. Fortschr. Roentgenstr. **88**: 401 (April), 1958.

The best determination of the shape and size of the pulmonary artery can be made by means of angiocardiography, but when this is impossible because of technical difficulties or sensitivity to iodine, other methods must be employed. One of these is tomography 24 hours after presacral injection of 1,500 to 2,000 ml. of air to give the air time to spread to the mediastinum. The left branch of the artery can be visualized best by frontal tomography at the depth of the trachea, while the right branch appears between trachea and aorta in lateral tomograms taken in the right paramedian plane.

LEPESCHKIN

de Coster, A., de Clerq, F., Bollaert, A., and Melot, G.: Angiocardiographic Alterations of Normal Lung Tissue with Reduction of Contra-Lateral Blood Flow. Acta cardiol. **13**: 75 (Fasc. 1), 1958.

A study of angiocardiograms of 63 patients with widespread pleuropulmonary disease revealed vascular changes in the remaining normal parenchyma, indicating adaptation of local blood flow by both, an increase of the speed of circulation, and an enlargement of the vascular bed. These 2 mechanisms may operate independently but the second appears to be the more efficient

one, since it is found frequently in the presence of significant circulatory impairment of the contralateral lung. The first, acceleration of blood flow, seems to come into action when increase in blood flow is insufficient for compensation. This may result in excessive adaptation and lead to clinical symptoms characteristic of arterial stasis. Variability in the observed angiocardiographic manifestations may be due to individual variations of the anatomic structure of the pulmonary vascular bed or to the failure of angiocardiograms to reveal increase of blood flow in certain areas of the pulmonary fields.

PICK

Cignolini, P.: Summary on the Use of Analytical Roentgen Kymography of the Heart and Blood Vessels. Fortschr. Röntgenstr. **88**: 328 (March), 1958.

Analytic high-speed multiple-slit moving-film kymography was developed by the author in 1930, and in 1950 it was combined with low-speed kymography in the form of polykymography. In this method, a low-speed kymogram (usually of the moving-slit type) is first taken to obtain an over-all picture of the movement pattern of the entire heart; in this picture 4 areas above the cardiac region, corresponding to the right and left atria, aorta and the left ventricle, are masked. The film is then lowered and 4 high-speed kymograms are registered in these areas simultaneously for a detailed analysis of the movement. The results of this study in various types of heart disease are summarized in detail.

LEPESCHKIN

SURGERY AND CARDIOVASCULAR DISEASE

McGoon, D. C., Edwards, J. E., and Kirklin, J. W.: Surgical Treatment of Ruptured Aneurysm of Aortic Sinus. Ann. Surg. **147**: 387 (March), 1958.

The case of a 26-year-old woman in whom a ruptured aneurysm of the aortic sinus was correctly diagnosed preoperatively and successfully repaired surgically is reported. The findings in this patient support the present concepts of the pathologic anatomy of aortic sinus aneurysms, namely, that at the site of the aneurysm the sinus wall is formed by surrounding tissues of either the right atrium or right ventricle and not by the aortic media. This tissue cannot withstand the aortic pressures and hence progressively gives way to form an aneurysm. Permanent surgical correction requires restoration of anatomic continuity between the aortic media and the heart at the level of the ring of the aortic valve. This can be accomplished with open cardiotomy and extracorporeal circulation. Surgery, therefore, should be undertaken in almost all instances in which the diagnosis of ruptured aortic sinus aneurysm has been established.

SAGALL

Taylor, W. J., Black, H., Thrower, W. B., and Harken, D. E.: Valvuloplasty for Mitral Stenosis during Pregnancy. J.A.M.A. **166**: 101 (March), 1958.

The additive effect of mitral stenosis and the usual hemodynamic alterations occurring in pregnancy produces a therapeutic problem of considerable complexity and importance. In such situations medical therapy, therapeutic abortion and surgical intervention are to be considered depending on the individual case. Valvuloplasty was carried out in 27 pregnant women with mitral stenosis. There were 3 maternal deaths. Two were believed to be unrelated to the associated pregnancy and 20 healthy children have resulted. There were 6 fetal deaths. Analysis of the causes of maternal death suggested more stringent selection of patients for surgery and elimination of those with free mitral insufficiency.

KITCHELL

Wade, G., Nicholson, W. F., and Jones, A. M.: Mitral Valvotomy and Pregnancy. Lancet **1**: 559 (March 15), 1958.

Twenty-seven women with mitral stenosis were studied, of whom 12 were operated on during pregnancy and 15 underwent pregnancy after a successful valvotomy. Operation was performed between the tenth and thirty-first week because of nocturnal dyspnea or severe effort dyspnea and radiologic evidence of severe pulmonary congestion. Assessment 6 months post partum showed that 10 of the 11 survivors were symptom free and 1 patient was functionally in group III. Eighty-nine such patients are recorded in the Anglo-American literature with 2 deaths, 5 abortions, and 84 living children. Pregnancy does not appear to increase operative risk and, in contrast to medical management, it does not increase fetal mortality. Sixteen pregnancies in 15 patients who had previously undergone valvotomy are reported. Only 1 child was lost owing to the cardiac condition. Despite these good results, symptoms due to severe pulmonary congestion were encountered in 3 of 10 patients placed in function group I after the operation, and in 5 of 6 patients in group II. A technically unsatisfactory operation even with reasonable functional improvement is unlikely to permit a trouble-free pregnancy. Fitness for pregnancy cannot be evaluated sooner than 6 months after operation.

but there has been a long interval from valvotomy to gestation, a careful reassessment for deterioration is necessary.

KURLAND

Paul, R. N. and Robbins, S. G.: Surgical Treatment for Endocardial Fibroelastosis or Anomalous Coronary Artery. Four Years' Experience with Poudrage. Am. J. Cardiol. 1: 694, (June), 1958.

On the theory that the functional difficulty in these 2 conditions is basically myocardial anoxia, 9 infants with fibroelastosis and 1 with anomalous left coronary artery received pericardial talc poudrage in an effort to augment the vascular supply of the left ventricular myocardium. A 2- to 4-year follow-up study of the 6 patients still surviving has shown improvement with respect to body growth, tendency to normalization of heart size, and the ability to omit digitalis. This result contrasts with the general experience in fibroelastosis of a 90 per cent mortality rate before age 2 years.

ROGERS

UNCOMMON FORMS OF HEART DISEASE

Gould, W. L.: Auricular Fibrillation. Report on a Study of a Familial Tendency, 1920-1956. Arch. Int. Med. 100: 916 (Dec.), 1957.

Twenty-two patients with a familial tendency to atrial fibrillation occurring through 5 generations of the same family are reported. This includes a 36-year continuing study among 113 members. It is pointed out that at the onset, atrial fibrillation may be paroxysmal and often escapes detection. These patients develop anxieties for lack of a diagnosis. Once the diagnosis becomes obvious in the paroxysmal variety, or atrial fibrillation becomes perpetual, management is usually quite easy. These patients generally are not in decompensation and hence should not be treated routinely for heart failure. Activity rather than inactivity should be prescribed. Minor postural changes frequently will terminate the paroxysmal variety. Sedation rather than quinidine and digitalis is the medication of choice. In general, the prognosis is good with a normal life expectancy.

KRAUSE

Scannell, J. G., and Grillo, H. C.: Primary Tumors of the Heart. A Surgical Problem. J. Thoracic Surg. 35: 23 (Jan.), 1958.

The authors describe 3 cases of primary tumors of the heart. The first was a left atrial myxoma that was successfully removed 22 months prior to the report. The second was a left atrial myxoma in a 9-year-old girl who died from cerebral emoblism prior to operation. The third was a right atrial fibrosarcoma (in a 7-year-old girl), successfully removed a year prior to this report. Both surgically treated patients were well at the time of the report. The clinical features of intracardiac myxoma are reviewed. This is the most common primary cardiac tumor, accounting for one third of reported cardiac neoplasms. Most myxomas occur in the left atrium, arising from the rim of the fossa ovalis on the interatrial septum. They are usually pedunculated and may cause ball-valve obstruction of the mitral orifice. The clinical picture is almost indistinguishable from mitral stenosis. Suspicion of the diagnosis may rest upon the absence of history of rheumatic fever, changes in symptoms and murmurs with changes in posture, syncope, and marked failure of response to medical treatment. Peripheral embolization during normal rhythm may also be suggestive. Right atrial tumors may cause similar obstruction of the tricuspid valve, resulting in right heart failure and a picture closely resembling constrictive pericarditis. Primary sarcomas, as a group, are the second most common primary cardiac tumors. They are most common in the right atrium. The left atrial myxoma operated on by the authors is the third successful case in the literature. It was done under hypothermia. The authors recommend that in the future primary cardiac neoplasms be removed by an open-heart method.

ENSELBERG

Lee, H. Y., and Kaufmann, W.: Cardiac Amyloidosis in the Aged. Arch. path. 64: 494 (Nov.), 1957

Seven patients with amyloidosis limited to the heart are reported. The condition appears to be more frequent in advanced age than is generally accepted. Amyloid in the heart under such circumstances is usually small in amount and may not produce clinical symptomatology, nor does it necessarily contribute to the patient's death.

MAXWELL

MacDonald, R. A., and Robbins, S. L.: Pathology of the Heart in the Carcinoid Syndrome. A Comparative Study. Arch. Path. 63: 103 (Feb.), 1957.

A comparative histologic study of the heart valves in patients with carcinoid syndrome (carcinoid fibrostenosis) is presented. The lesions are shown to be unlike those found in the heart in

congenital, degenerative, infectious, and collagen diseases. In a summary of reported cases it was noted that the pulmonic and tricuspid valves have been those chiefly affected. Grossly, a pearl-gray thickening of the pulmonic and tricuspid valve cusps has been noted, binding the edges of the cusps together in many cases, and causing stenosis and occasionally regurgitation. Associated hypertrophy of the right ventricle has often been seen. The lesions of carcinoid fibrostenosis may be differentiated from other conditions by use of phloxine-methylene blue and elastica stains. A peculiar fibrous tissue devoid of elastic fibers was present upon relatively intact endocardium in the 3 hearts in which valvular lesions were present. Large numbers of tissue mast cells were seen in the affected valvular endocardium and in contiguous fibrous tissue. It was found in this study that cases of carcinoid tumor that had not produced extensive metastases were not associated with valvular lesions, and that not all cases with extensive metastases were associated with valvular changes. Consideration was given to the possible role of serotonin producing metastases in production of the valvular lesions.

MAXWELL

Roberts, H. J.: The Clinical Problem of Adiposity of the Heart and Cardiac Enlargement of Undetermined Etiology. Dis. Chest **31**: 84 (Jan.), 1957.

Attention is directed to the problem of fatty infiltration of the heart. A probable case of "adiposity of the heart" diagnosed clinically in a living 30-year-old man is presented. The patient was an athletically active individual who had gained 50 pounds in weight over a 2-year period, with concomitant enlargement of the heart noted in routine chest x-rays. Past history, physical examination, and laboratory studies, including electrocardiograms and ballistocardiograms, seemed to rule out the usual causes of cardiac enlargement (rheumatic, hypertensive, congenital, and arteriosclerotic heart disease; cardiac complications of other diseases; myocarditis, endomyocardial fibroelastosis, etc.). The only abnormal finding was electrocardiographic evidence of right bundle-branch block. On a vigorous weight reduction program the heart size decreased radiographically, although the bundle-branch block persisted. This condition should be suspected in patients demonstrating unexplained cardiomegaly in the presence of a recent rapid and profound weight gain and in the absence of the stigmata of the other causes of heart disease. It may be asymptomatic or manifested by heart block and congestive heart failure.

MAXWELL

Sulser, U. J.: The Clinic and Pathologic Anatomy of Kyphoscoliosis with Particular Reference to Life Expectancy. Cardiologia **32**: 231 (April), 1958.

The case histories and anatomic findings were reviewed of 246 instances of kyphoscoliosis and scoliosis, found in autopsy material of 10,877 cases (2.26 per cent). In 54 cases (0.46 per cent) the condition was severe. Kyphoscoliosis with convexity to the right is much more common than left convexity (38:16). Females are more often affected than males (25:19). Kyphoscoliosis produces characteristic deformities of the thorax and changes in the lungs consisting in emphysema, atelectasis, and nonspecific inflammation. Tuberculosis is rare and no case of pulmonary arterial sclerosis was present in the material. The heart usually reveals right ventricular hypertrophy with or without dilatation. From the prognostic viewpoint, 2 clinical types can be recognized according to the occurrence of death shortly after the first episode of heart failure, or following recurrent attacks of failure.

PICK

VALVULAR HEART DISEASE

Ross, R. S., McKusick, V. A., and Harvey, J. C.: The Problem of Fever in Patients with Valvular Heart Disease. J. A. M. A. **165**: 1 (Sept. 7), 1957.

The co-existence of fever and valvular disease presents a problem in differential diagnosis and management which is quite different from that associated with either condition alone. There is a relatively high frequency of occurrence of this problem in general hospital practice. The authors reviewed 25 such cases that occurred in the Johns Hopkins University Hospital between 1951 and 1954. The causes of fever were listed as: acute rheumatic fever, postcommissurotomy syndrome, bacterial endocarditis, drug fever, embolism, and miscellaneous. Under this last grouping are included congestive heart failure, hemoglobin pneumonia, systemic lupus erythematosus, atrial myxoma. Bacterial endocarditis should properly be given first consideration when fever and a heart murmur co-exist, but one should also direct attention to other conditions that closely simulate it. Where a differentiation between rheumatic activity and bacterial endocarditis cannot be made with certainty, and where the patient is gravely ill, therapy should be directed at both diseases.

KITCHEL

Evans, W., and Short, D. S.: Pulmonary Hypertension in Mitral Stenosis. Brit. Heart J. **19**: 4[illegible] (Oct.), 1957.

The pulmonary vessels were studied histologically in all and by postmortem arteriography in 12 of 24 persons with mitral stenosis. Focal changes were present in every case and diffuse changes consisting of absence of opaque material from the finest branches throughout the lung in 6 of the 12 studied by arteriography. The focal changes were characterized histologically by intimal thickening, thrombosis or abnormal bronchopulmonary anastomoses. The diffuse changes consisted of widespread intimal proliferation, hypoplasia of the media, and refractory arterial contraction, findings similar to those seen in primary pulmonary hypertension. These findings were associated with right ventricular hypertrophy. This latter group was seen predominantly in women, produced disablement at a young age, and was characterized by a small pulse, raised venous pressure, prominent atrial wave, loud pulmonic second sound, a sound early in systole, and occasionally a Graham Steell murmur. Right atrial and ventricular hypertrophy were seen in the electrocardiogram and prominent pulmonary artery and main branches radiologically. The pulmonary artery pressure was disproportionately increased and the cardiac output reduced. Progressive and irreversible vascular obstruction accounts for persistent pulmonary hypertension in mitral stenosis and in this type of patient mitral valvotomy is unlikely to produce material or lasting benefit.

SOLOFF

Fleming, H. A., and Robinson, C.L.N.: Pulmonary Ossification with Cardiac Calcification in Mitral Valve Disease. Brit. Heart J. **19**: 532 (Oct.), 1957.

The authors report 8 patients with isolated mitral valve disease and disseminated pulmonary ossification, 7 of whom had massive calcification of the mitral valve or left atrium or both. Seven were men and all had high pulmonary pressures and low cardiac ouputs. Pulmonary ossification was present in all zones but was most dense in the lower, particularly on the right. Kerley's lines were present although none of the patients at any time had symptoms of pulmonary congestion. Nevertheless, these lines were interpreted as evidence of pre-existing pulmonary venous congestion and subclinical pulmonary edema.

SOLOFF

Belcher, J. R.: Restenosis of the Mitral Valve. Brit. Heart J. **20**: 76 (Jan.), 1958.

The author classifies restenosis of the mitral valve into true stenosis, which is said to occur after 1 or both commissures have been completely opened, and false restenosis when neither commissure is said to have been divided beyond the area of insertion of the papillary muscles. The author reports 8 patients operated upon for false restenosis and 4 for true restenosis. In 10, the commissure could not be divided by the normal method. An incision was made in the wall of the left ventricle near the apex and the sound was passed through this incision until it engaged the mitral orifice. The blades were then opened first to 4 and then to 5 cm. Separation of both commissures was achieved in all but 1. One patient died later of a massive cerebral embolus. Eight had results classified as good and 3 as fair. Mitral regurgitation was produced in 4. The author states that the results as yet are not as good as might have been expected from the efficacy of the division of the commissures.

SOLOFF

Harris, T. N., Friedman, S., and Tang, J.: The Appearance of New Cardiac Murmurs in Patients Having Rheumatic Heart Disease with No Concomitant Evidence of Rheumatic Activity Am. J. Med **23**: 748 (Nov.), 1957.

Clinical data, measurements of acute phase reactants, and results of streptococcal serologic tests are reported in 4 children in whom evidence of extension of heart disease was found to be unassociated with an episode of rheumatic fever. In each patient, a new cardiac murmur was observed when the sedimentation rate, C-reactive protein and mucopolysaccharide tyrosine, antistreptolysin O titer and antihyaluronidase had been stabilized for considerable periods. Two additional children are reported in whom both phase reactants and streptococcal antibodies were within normal limits but in whom the findings of progressive cardiac enlargement gave indication of low-grade rheumatic activity.

KURLAND

Goodwin, J. F., Rab, S. M., Sinha, A. K., and Zoob, M.: Rheumatic Tricuspid Stenosis. Brit. M. J. **2**: 1384 (Dec. 14), 1957.

Twenty-one proved cases of rheumatic tricuspid disease (13 diagnosed clinically and 8 by necropsy) are discussed. The clinical picture varied depending upon the complicating valvular disease that co-existed. Particular stress was placed upon the degree of right atrial enlargement determined radiologically. This finding was out-

side the normal range in practically all of the cases. Right ventricular dominance was best determined by the electrocardiogram. The authors demonstrated that right atrial enlargement but little right ventricular hypertrophy was particularly characteristic of tricuspid stenosis. Electrocardiographically, a high percentage of these patients also demonstrated right atrial P waves and prolongation of the P-R interval. Cardiac catheterization was performed in 8 patients. In 2 the catheter could not be advanced from the right atrium into the right ventricle. In the 6 patients in whom a complete catheterization was accomplished, a gradation of from 5 to 25 mm. of mercury was recorded in diastole across the tricuspid valve. The fact that tricuspid murmurs usually become louder during inspiration and mitral murmurs do not, is again emphasized. The authors conclude that tricuspid incompetence is a very common but not invariable accompaniment of tricuspid stenosis. This factor must naturally be taken into account when patients are being considered for valvulotomy of a stenotic tricuspid valve.

KRAUSE

Peery, T. M.: Brucellosis and Heart Disease. IV. Etiology of Calcific Aortic Stenosis. J.A.M.A. **166:** 1123 (March 8), 1958.

Because of inconsistencies in the popular theories regarding the etiology of calcific aortic stenosis, another explanation has been sought for this form of valvular heart disease. There is evidence to the effect that this is often a residuum of brucellar endocarditis, chiefly due to the *Brucella abortus* strain. The evidence presented shows that such a valve lesion has in a number of cases followed a febrile disease diagnosed as brucellosis. In fatal brucellosis, chronic endocarditis is almost a constant finding. This primarily effects the aortic valve and there is a tendency for the ulcerated valve to heal and calcify. The granulomatous lesions in other organs during brucellosis closely resemble the valve lesions in calcific aortic stenosis. The sex incidence of calcific aortic stenosis is unusual and corresponds with that of brucellosis rather than that of rheumatic fever. Some patients with such valve lesions show a high titer of agglutinins against Brucella in their serum. Brucellosis may well be the chief cause of calcific aortic stenosis on the basis of pathologic, clinical, and immunologic studies; and such observations open up new vistas for the prevention of heart disease.

KITCHELL

Yu, P. N., Nye, R. E., Jr., Lovejoy, F. W., Jr., Schreiner, B. F., and Yim, B. J. B.: Studies of Pulmonary Hypertension. IX. The Effects of Intravenous Hexamethonium on Pulmonary Circulation in Patients with Mitral Stenosis. J. Clin. Invest. **37:** 194 (Feb.), 1958.

Twenty-seven patients with mitral stenosis were studied to evaluate the effects of hexamethonium on pulmonary pressures. The drug was administered through a catheter into the pulmonary artery in doses sufficient to produce an initial depression of 30 mm. Hg in brachial artery systolic pressure. Although there were statistically significant decreases in the pressure of the femoral artery, pulmonary artery, and pulmonary "capillaries," there were no statistically significant changes in the cardiac index, stroke index, heart rate, pulmonary artery-to-pulmonary capillary pressure gradient, and pulmonary vascular resistance. In over half the cases the pulmonary artery pressure declined. This effect occurred usually within 10 minutes of the start of the injection and at the same time as, or shortly following, the fall in femoral artery pressure. The decrease in pulmonary "capillary" pressure was roughly proportional to the decrease in femoral artery pressure, but the changes here were unrelated to changes in flow. There was, in short, a paradox of reduced pulmonary "capillary" pressure without change in flow. Possible explanations include changes in left ventricular diastolic pressure and decreases in transport of blood through intrapulmonary vascular shunts. Intravenous hexamethonium was used clinically in the treatment of acute pulmonary edema in 3 patients with mitral stenosis and in 2 patients in whom pulmonary edema developed during cardiac catheterization. The clinical importance of this drug is indicated by the successful use of it in the treatment of acute pulmonary edema.

WAIFE

Barlow, J., and Shillingford, J.: The Use of Amyl Nitrite in Differentiating Mitral and Aortic Systolic Murmurs. Brit. Heart J. **20:** 162 (April), 1958.

An apical systolic murmur may be due to mitral regurgitation, aortic stenosis, or both lesions. The authors used the phonocardiographic and auscultatory changes produced by amyl nitrite to distinguish these three causes of the murmur. That of mitral regurgitation diminishes during the first 20 seconds after inhalation of the drug, whereas that of aortic stenosis remains unchanged or increases slightly. Then the murmur of mitral regurgitation slowly returns to its original intensity whereas that of aortic steno-

reaches its maximum intensity for the following 15 to 20 seconds and slowly returns to its original intensity over an equal length of time. When both lesions are present, the mitral regurgitant murmur fades for the first 20 seconds and then the murmur increases in intensity. Clinically, this is best recognized by 2 observers listening simultaneously, one at the apex and the other outside the apex toward the axilla.

SOLOFF

Hancock, E. W. Madison, W. M., Jr., Proctor, M. H., Abelmann, W. H., and Starkey, G. W. L.: Aortic Stenosis of No Physiologic Significance. New England J. Med. **258:** 305 (Feb. 13), 1958.

Seven patients are reported and discussed because although they had clinical evidences of aortic stenosis and were considered for aortic valve surgery, it was shown that in actuality they did not have any significant narrowing of the aortic valve. In 5 cases this conclusion was based upon studies obtained from catheterization of the left side of the heart by right posterior transthoracic puncture of the right atrium and in 2 by postmortem examination. Although each patient presented many of the clinical features characteristic of aortic stenosis, the clinical picture in each was in some respect atypical. In 5 cases the clinical picture was due to coronary artery disease with myocardial infarction and in 2 cases to mitral valve disease. These cases illustrate the fact that patients with signs and symptoms suggestive of severe aortic stenosis may be suffering from other types of heart disorders. In order to avoid ill-advised aortic surgery on patients of this type catheterization of the left side of the heart to establish the correct diagnosis should be done whenever surgery of aortic stenosis is being considered and there is uncertainty about the degree of aortic stenosis present.

SAGALL

McGuire, J., Scott, R. C., and Gall, E. A.: Chronic Aortitis of Undetermined Cause with Severe and Fatal Aortic Insufficiency. Am. J. M. Sc. **235:** 394 (April), 1958.

Aortic insufficiency of a hitherto undescribed type leading to rapidly progressive and fatal congestive failure has been observed in 5 patients since 1950. None of the usual etiologies for this valvular lesion was found by clinical study or by postmortem examination. The lesions detected in the aorta resembled those encountered in syphilitic aortitis but no other clinical or pathologic stigmata of this disease could be demonstrated. The histopathologic findings were identical in the 5 cases with intimal thickening, destruction of elastica with collagen replacement and scarring, thickening of adventitia, coagulation necrosis in 2 cases, and thickening and retraction of the aortic cusps. Some inflammatory exudation and perivascular cuffing were noted within the media and adventitia. The serologic tests for syphilis were negative with no prior history of this disease elicitable. The age range of 15 to 37 years was young for syphilitic aortitis. It is suggested that cases resembling syphilitic aortitis may be the result of other causes and that a search for other etiologic factors, none of which was found in these 5 patients, may be rewarding.

SHUMAN

Brusca, A., Carbagni, R., Solerio, F., and Gavosto, F.: Central Blood Volume in Mitral Disease. Arch. mal. coeur **51:** 51 (Jan.), 1958.

In 38 patients with mitral disease and 24 normal persons the pulmonary blood volume and the mean circulation time were studied by means of dye dilution (T-1824). A positive linear correlation between this volume and the cardiac index was found in both groups of persons. In mitral disease this volume had absolute values that are still within normal limits, but must be considered as elevated in relation to the diminished cardiac output.

LEPESCHKIN

Watt, H. J., and Barrie, H. J.: Long-Standing Thrombosis of the Pulmonary Arteries Complicating Valvulotomy for Mitral Stenosis. J. Thoracic Surg. **34:** 804 (Dec.), 1957.

The authors describe 3 patients with mitral stenosis in whom circulatory collapse appeared during or just after mitral valvulotomy and in whom death occurred shortly afterward. Necropsy examination showed the presence of long-standing occlusion of the right pulmonary artery in each patient. A review of the literature and a study of 6 additional cases of pulmonary artery thrombosis led to the conclusion that the occlusion was almost always due to accretions of thrombi on previous emboli, particularly in the patients with mitral stenosis. Also it appeared that the lesion affected the right pulmonary artery much more often than the left. It was difficult to establish the diagnosis in patients with severe disability from mitral stenosis since many features were common to both conditions (cyanosis, dyspnea, hypertrophy and dilatation of the right heart, accentuated second pulmonic sound, and right heart failure). Roentgenologic findings such as loss of pulmonary arterial pulsation and unexpected clarity of lung field or sudden increase in size of the right pulmonary artery can

be of help. Inability to enter the artery during cardiac catheterization can also help in diagnosis. Probably the best approach to diagnosis is angiocardiography. The authors doubt whether mitral valvulotomy is justified in the presence of pulmonary artery thrombosis.

ENSELBERG

Anschütz, F., and Drube, H. C.: The Diastolic Fall of Pressure and the Accelerated emptying of the Arterial Reservoir in Calcified Aortic Sclerosis. Ztschr. Kreislaufforsch. **46**: 824 (Nov.), 1957.

Intraarterial pressure measurements in the femoral artery showed that in persons with aortic sclerosis the pressure in diastole fell exponentially and more rapidly than in normal persons. This was considered to be due to a higher coefficient of elasticity of the aortic reservoir and also to the stiffness of the peripheral arterioles, which showed no decrease of their diameter with a fall of blood pressure. Both factors led to a more rapid emptying of the arterial reservoir.

LEPESCHKIN

Joly, F., Carlotti, J., and Forman, J.: "Moderate" Mitral Stenosis, Pure or with Mitral Insufficiency. (Clinical and Hemodynamic Study of 36 Cases before and after Operation.) Arch. mal. coeur **50**: 873 (Oct.), 1957.

Moderate mitral stenosis (mitral area of 2 cm.^{2} or more), if pure (10 patients), showed the same clinical and auscultatory signs as tight stenosis. When combined with mitral regurgitation (26 patients), it showed a much higher incidence of intense holosystolic apical murmurs than tight stenosis, where these murmurs were absent except in marked valvular calcification. However, no relation was found between the intensity of the regurgitant stream, as felt by the surgeon, and that of the murmur. Radiologic detection of systolic expansion of the left atrium was also much more common in moderate stenosis. A frank right ventricular hypertrophy and strain pattern in the electrocardiogram was exceptional in moderate stenosis, especially if combined with regurgitation; if this pattern was absent in spite of a mean pulmonary artery pressure of 45 mm. or more, mitral regurgitation, or aortic stenosis was always present. A single large wave in the pulmonary capillary pulse was seen in over half of the patients with moderate stenosis with regurgitation, but in none of 199 patients with tight stenosis, with or without regurgitation. Atrial fibrillation was also found in more than half of these patients, and calcification of the valves was more common. The incidence of lasting improvement after operation was much smaller in moderate than in tight stenosis with comparable functional impairment.

LEPESCHKIN

Donzelot, E., DeBalsac, R. H., and David, A.: Aggravation of Mitral Heart Disease Following Pregnancy. A Statistical Study of 233 Cases. Am. J. Cardiol. **1**: 51 (Jan.), 1958.

The influence of 500 pregnancies on the course of the heart disease in 233 women was observed for periods up to 5 years after delivery. Evidence of cardiac deterioration appeared within 6 months postpartum in 29 per cent, within 7 to 12 months postpartum in 11 per cent, and during the next 1 to 4 years in 17 per cent. The aggravation of the heart condition consisted most commonly of diminished effort tolerance, and in 29 instances rheumatic fever was reactivated postpartum. In another group of 193 mitral patients, the cardiac status deteriorated during pregnancy in 62 per cent, but on adequate therapy the great majority of these women were not disabled. Pregnancy is viewed as a "stress" which is well tolerated by the normal but not by the rheumatic heart.

ROGERS

Hadorn, W., Luthy, E., and Stucki, P.: Various Manifestations of Pulmonic Stenosis. Cardiologia **31**: 5 (Fasc. 1), 1957.

Hemodynamic and clinical findings were compared in 20 patients with various types of pulmonary stenosis, in 17 instances congenital, and in 3 acquired. The former included patients with intact ventricular septa, and tetralogies as well as patients with associated atrial septal defects (trilogies); the latter were assumed to have developed in 1 patient with ventricular septal defect as a consequence of a healed subacute bacterial endocarditis and in 2 patients from external compression of the pulmonary artery by tumor masses and adhesive pericarditis respectively. The patients were divided into 2 groups on the basis of the magnitude of the pressure gradient across the pulmonary valve. Only in patients with large gradients (77 to 190 mm. Hg.) is valvulotomy to be recommended. In patients with trilogy with small gradients the clinical syndrome is dominated by the interatrial communication and hence repair of the latter is indicated rather than valvulotomy. This was performed in 4 instances with good results.

PICK

Burwell, C. S.: The Special Problem of Rheumatic Heart Disease in Pregnant Women. J. A. M. A. **166**: 153 (Jan. 11), 1958.

The course of 236 patients with rheumat-

heart disease who went through 298 pregnancies is discussed. The predominant lesion in these rheumatic heart disease cases was mitral stenosis. A quantitative analysis of the added burden imposed by pregnancy points out that about 15,000 extra beats are made per day and the maximum stress is passed some weeks before term. There were 3 deaths. Four years later only a few cases were worse. Most patients were in the same functional classification as before the pregnancy and 27 patients were better. Thus, there was no evidence that pregnancy accelerated the course of heart disease. The management of heart disease in pregnant women is a matter of preventing and controlling burdens that are to some degree avoidable or removable. These burdens are as follows: physical activity, emotional stress, ectopic rhythms with tachycardia, anemia, obesity, infections, hyperthyroidism, infusions or transfusions, and increases in sodium intake or retention. The success of reducing this burden depends on the cooperation of the patient, the persuasiveness of the doctor, and the availability of appropriate services in the community. The authors point out 3 approaches to management of the pregnant woman with rheumatic heart disease. First is termination of pregnancy, a poor decision, as fetal mortality is 100 per cent and the risk to the mother (both physically and psychologically) is appreciable. Secondly, it is thought by the author that it is almost never necessary to perform commissurotomy during the course of the pregnancy. The third method is that of conservative medical management, which the author believes is the best of all.

KITCHELL

Wood, P.: Aortic Stenosis. Am. J. Cardiol. 1: 553 (May), 1958.

A detailed analysis is presented of 250 consecutive patients with aortic stenosis observed by the author over the past 7 years. Fifty-four were of congenital origin; 196 were apparently rheumatic, and serious aortic incompetence was found in 30 of these. The rheumatic patients were aged 19 to 79 years, averaging 46; two thirds were men. Symptoms were noted in 143 individuals—angina pectoris in 70 per cent, syncope on effort in 33 per cent and left heart failure in 45 per cent with dyspnea heralding this event. The principal physical findings were a characteristic systolic murmur heard at the apex and base, accompanied in 80 per cent by a thrill; an aortic diastolic murmur in two thirds of the rheumatic cases which when loud usually indicated serious aortic incompetence; an aortic ejection click in most of the less severe cases; a diminished and delayed aortic second sound, paradoxically split in 25 per cent; a hyperdynamic apical impulse with invisible carotid pulsation and small prolonged peripheral pulses.

The electrocardiogram remained unchanged until the stenosis was severe when left ventricular preponderance with T-wave inversion was found in 80 per cent, and left bundle-branch block appeared in 14 per cent. Atrial fibrillation occurred in 13 per cent, all of whom had associated but non-dominant mitral valve disease. The classic roentgenologic changes were a small aortic knuckle, post-stenotic dilatation of the ascending aorta, valve calcification in 80 per cent of patients over age 30, and little or no left ventricular enlargement before the advent of heart failure. Intrabrachial arteriograms, performed routinely in severe cases, showed systolic pressures averaging 120 mm. Hg with pulse pressures of 30 to 50 mm.Hg, slow pressure ascent to the anacrotic shoulder averaging 450 mm. Hg per second (normally 1,000), low anacrotic shoulder, delayed maximum pressure rise of 0.20 to 0.28 second (rate corrected), delayed dicrotic notch and absence of a positive dicrotic wave. The maximum systolic pressure gradient across the aortic valve varied according to the degree of stenosis and to the forward stroke flow, ranging from 30 to 200 mm. Hg or more in severe lesions. The cardiac output in 16 severe cases free from heart failure averaged 5.3 L./minute, and 5 cases in failure average 3 L./minute. In 80 patients having valvotomy, the results were good in 43, indifferent in 21, and fatal in the remainder; a comparable group treated medically fared considerably less well. Criteria for the selection of patients for surgery are outlined, and the preoperative evaluation of accompanying disorders is discussed with emphasis on hemodynamic findings.

ROGERS

Bentivoglio, L., Uricchio, J. F., and Likoff, W.: The Paradox of Right Ventricular Enlargement in Mitral Insufficiency. Am. J. Med. **24:** 193 (Feb.), 1958.

Four patients with chronic rheumatic heart disease in whom isolated mitral insufficiency was accompanied by predominant right ventricular hypertrophy were studied by cardiac catheterization and subjected to surgical exploration of the mitral valve. All demonstrated the manifestations of right heart failure. Atrial fibrillation and right ventricular hypertrophy were seen on electrocardiogram, and enlargement of the pulmonary artery, the right ventricle, and the left atrium were seen on roentgenogram. Cardiac catheterization revealed a reduced cardiac output and a marked resistance to pulmonary blood flow. Path-

ologic review revealed medial hypertrophy and intimal proliferation in both the large and small arteries of the lung. No mitral stenosis was present. It is suggested that a tonic atrium transmits the burden of mitral insufficiency from the left to the right ventricle through its effect on the pulmonary vascular tree.

KURLAND

Genkins, G., Moscovitz, H. L., Gordon, A. J.: Dynamics of Valvular Pulmonic Stenosis Studied by Needle Puncture of Pulmonary Artery and Right Ventricle. J. Appl. Physiol. **12**: 437, (May), 1958.

This report presents the hemodynamic data in 10 patients with valvular pulmonic stenosis studied by direct needle puncture of the right ventricle and pulmonary artery in the open chest at the time of thoracotomy. Pressure pulses were recorded simultaneously and at equal sensitivity. The cardiac cycle in valvular pulmonic stenosis differs from the normal by the marked abbreviation or complete absence of the phases of isometric contraction and relaxation. The right ventricle contracts in an abnormal manner, with a sharply peaked pressure pulse contour. The pulmonary artery curve shows an early systolic dip. Only slight reduction of the right ventricular pressure occurred following surgery in some patients. However, both the maximum and mean right ventricular-pulmonary artery ejection gradients were approximately halved.

RINZLER

VASCULAR DISEASE

DeBakey, M. E., Morris, G. C., Jr., Jordan, G. L., Jr., and Cooley, D. A.: Segmental Thrombo-Obliterative Disease of Branches of Aortic Arch. J.A.M.A. **166**: 998 (Mar. 1), 1958.

Segmental thrombo-obliterative disease of the branches of the aortic arch (also known as the aortic arch syndrome, pulseless disease, Takayasu's disease, and Martorell's syndrome) is the clinical entity resulting from occlusion of 1 or more of the great vessels arising from the aortic arch. It manifests itself by ischemic disturbances and the absence of pulses in the head, neck, and upper extremities. In these cases the thrombo-obliterative process tends to be fairly well localized and is segmental in character. The occlusive lesion beginning near or at the origin of the great vessels arising from the arch rarely extends beyond the bifurcation of the common carotid arteries or the supraclavicular portion of the subclavian arteries. This permits direct surgical attack upon the lesion in re-establishing normal circulation. The authors discuss surgical treatment as successfully applied in 2 patients: one by the use of by-pass and the other by a thrombo-endarterectomy. In both instances there was complete relief of symptoms and restoration of normal circulation.

KITCHEL

Dubost, C. and Chaubin, F.: Abdominal Aortic Aneurysms. Arch. mal. coeur **51**: 172 (Fe), 1958.

Of 16 patients with aneurysm submitted to operation, the wrapping method was used in 2 cases because of advanced age and recent coronary thrombosis or because aortic clamping caused immediate cardiac failure. Of 14 patients operated by excision and graft, 1 died of pulmonary embolism while another died because of rupture of an Ivalon graft. The other patients had a graft of Nylon or a homograft, with excellent results.

LEPESCHKIN

Burman, S. O., and Geratz, J. H. D.: Non-Hemorrhagic Cleavage of the Aorta. Ann. Surg. **147**: 571 (April), 1958.

Three patients are described in whom severe noninflammatory degeneration of the walls of several arteries of the aorta led to spontaneous nonhemorrhagic cleavage of the aorta. In 2 patients death was considered to have resulted solely from the consequences of the spontaneous cleavage. In 1 patient cleavage led to functional obstruction of the left common iliac artery resulting in a clinical picture of arterial occlusion indistinguishable from that due to other causes. It is pointed out that aortic cleavage necessarily is preceded by medial degeneration characterized by the loss of muscle and elastic elements and the accumulation of abnormal amounts of ground substance.

SAGALL

Poole, J. C. F., Sanders, A. G., and Florey, H. W.: The Regeneration of Aortic Endothelium. J. Path. & Bact. **75**: 133 (Jan.), 1958.

These authors traumatized the aortic endothelium of young rabbits by passing a brass rod through the femoral artery into the abdominal aorta of the rat. They followed the pathologic picture of endothelial regeneration in over 200 rats sacrificed from one-half hour to 232 days following operation. The aortas were mounted by an ingenious procedure and the endothelial layer was separated from the media and adventitia and endothelial cells were stained with silver so that borders were easily identifiable. The process of reendothelialization was then followed in this group of animals and related to the passage of time. The initially traumatized area was first

covered with platelets and leukocytes. No thrombus developed. The endothelium regenerated from the borders of the traumatized area and gradually extended over the greater portion of the raw surface. This process required 7 to 8 months for complete endothelialization. Endothelial cells appeared to arise from mitotic division of preexisting endothelial cells. The authors believe that endothelium is not formed from any other tissue and that there is nothing unusual about its nuclear division.

HARVEY

Dible, J. H.: Organisation and Canalisation in Arterial Thrombosis. J. Path. & Bact. **75:** 1 (Jan.), 1958.

A pathologic study was made of the organization of arterial thrombi. The author demonstrates that organization and canalization are distinct processes in origin and purpose within the vascular channel within the internal elastic lamina, and that the process is not one in which there is an invasion of the thrombus by the intrinsic vessels of the arterial wall. The author shows 2 sharply separated sets of vessels by means of formalin injection, distention, and reconstruction of models from the sections. These vessels are separated from those of the outer and middle coats of the wall; the vessels that canalize the thrombus arise within the elastic lamina and also from the thrombus material itself. These vessels are at right angles to each other; those within the canalized thrombus always horizontal to the thrombus and running in the direction of the artery, and the vessels from the wall perpendicular to the thrombus. The lamina appears to be an impassable barrier to the ingress of vessels from the outer wall. The author gives his ideas of the steps in the organization and canalization of the thrombus—first being the development of vascular channels within the thrombi, and secondly the liquefication and ingestion of the loose component part of the thrombus structure, leaving a sponge work of fibrin into which endothelial cells proliferate, forming endothelialized channels, but the author thinks that the endothelial cells do not come from the endothelial lined channels within the vessel in which the thrombus is contained. Serial sections show no continuity with the lining of the endothelium of the vessel, and the author believes that the endothelial cell origin within the thrombus may be free from circulating endothelial cells grafting themselves upon a new fibrin network and that these cells are brought into the fibrin network by eddy currents of blood within the interspaces of the thrombus. In his serial sections he shows no growth of endothelium into the area below the internal elastic lamina, and he believes that this set of vessels does not contribute to recanalization of arterial thrombi.

HARVEY

Kinmonth, J. B., Taylor, G. W., Tracy, G. D., and Marsh, J. D.: Primary Lymphoedema. Clinical and Lymphangiographic Studies of a Series of 107 Patients in Which the Lower Limbs Were Affected. Brit. J. Surg. **45:** 1 (July), 1957.

The authors have studied 107 patients with lymphedema of the lower limbs and concluded that patients with primary lymphedema can be divided according to the age at which the disease becomes manifest into 3 groups—congenita, praecox, and tarda. In all groups the underlying pathology consists in maldevelopment of lymphatics. The onset of the disease is earlier in cases with more marked or widespread defects of lymphatic structure. A familial tendency was present in 17 per cent of cases, a finding which lends support to the concept of a developmental error. In 17 patients there was a history of a precipitating factor, usually something which might have caused transient edema in a normal subject. Lymphangiograms have allowed division into 3 main groups according to the state of the lymphatic trunks. These are hypoplasia, dilatation and tortuosity ('varicose lymphatics'), and aplasia. The morbid anatomy revealed by lymphangiography in primary lymphedema is different to that found in cases of acquired obstructive lymphedema.

MAXWELL

Exton-Smith, A. N., and Crockett, D. J.: Nature of Oedema in Paralyzed Limbs of Hemiplegic Patients. Brit. M. J. **2:** 1280 (Nov. 30), 1957.

Edema of a paralyzed limb was noted in 15 per cent of patients with hemiplegia. It was usually more marked in the upper rather than in the lower limb and may even be confined to the hand. The edema fluid has a high protein content. The most important factor to cause it was the lack of adequate lymphatic drainage of protein due to muscular inactivity. The retained protein reduces the effective colloid osmotic pressure of the plasma and lends to the accumulation of fluid in the extravascular extracellular compartment. Removal of edema fluid was promoted by the encouragement of lymphatic drainage. Edema fluid was collected for study by the use of small Southey-type needles. When edema occurred in the leg and arm, the protein content was lower in the leg indicating that some of it was due to congestive heart failure or venous thrombosis. Contributing factors in the production of edema were increased venous pressure produced by ly-

ing on the affected arm, the dependent position of the arm when it was flaccid, splinting, venous thrombosis, and congestive heart failure. Usually the skin temperature was higher in the hemiplegic leg or arm that showed edema. This would seem to be good evidence for arteriolar dilatation due to disturbance of vasomotor regulation in the brain. No evidence for increased capillary permeability to proteins could be demonstrated in this study. Hemiplegic patients who are confined to bed and who develop edema in the paralyzed leg and not in the arm, should be suspected of having thrombophlebitis of the leg.

KRAUSE

Rose, G. A.: The Natural History of Polyarteritis. Brit. M. J. 2: 1148 (Nov. 16), 1957.

One hundred eleven patients with polyarteritis are reviewed. These are divided into the following categories: (1) 32 patients with polyarteritis nodosa who have lung involvement, (2) 66 patients with polyarteritis nodosa without lung involvement, and (3) 13 patients of a heterogeneous nature. Ascertaining lung involvement is important, for as a rule, if lung lesions occur at all, almost always they precede lesions in other organs (sometimes by years). Furthermore, they are commonly associated with characteristic lesions in other organs of a type not seen in cases without lung involvement. Generally a relationship has been noted between the onset of the disease and preceding respiratory infection. It was also observed that the blood pressure was normal during the acute stage of the lesion, but began to rise with healing and fibrosis. This would seem to indicate that when hypertension occurs in polyarteritis, it is the result of renal (arterial or glomerular) fibrosis. Although the separation on the basis of lung involvement might be warranted clinically, it is probably true that we are dealing with variants of the same disease.

KRAUSE

Richards, R. L.: Prognosis of Intermittent Claudication. Brit. M. J. 2: 1091 (Nov. 9), 1957.

The author reviews 60 patients (55 men and 5 women) with intermittent claudication. Of this group, 58 had arteriosclerosis obliterans and 2 had thromboangiitis obliterans. As a rule, the intermittent claudication is usually a reflector of diffuse vascular disease. This is proved by the high incidence of ischemic heart disease and cerebrovascular disease that subsequently developed. In a 5 year observation period, 17 (28 per cent) of the group died. Thirteen of the 17 deaths were due to cardiovascular disease. Of the 43 survivors 39 per cent developed angina and of the total group 57 per cent developed either anginal or congestive heart failure. Of the 60 patients with intermittent claudication, 6 developed gangrene of the extremity requiring amputation. Claudication is often the first symptom of generalized cardiovascular disease, which may be fatal in a few years. The prognosis for life is not as serious as that of angina pectoris or myocardial infarction from which the patient has made a good immediate recovery. The outlook for the involved limb is relatively good and as time goes on, the patient is more likely to be disabled by the effects of coronary artery disease or cerebrovascular disease.

KRAUSE

Billig, D. M., and Shadle, O. W.: Mechanism of Reflex Bradycardia Which Follows Sudden Closure of an Arteriovenous Fistula. Proc. Soc. Exper. Biol. & Med. 95: 680 (Aug.-Sept.), 1957.

Reflex bradycardia occurs with the closure of an arteriovenous fistula. The efferent limb of the reflex is the vagus, and the authors attempt to describe the afferent limb of the reflex and the mechanism which initiates the reflex bradycardia. Dogs were used in whom the right vagus was functionally intact and in whom the carotid sinus and the aortic arch could be functionally denervated. The arteriovenous fistulas were produced between both femoral arteries and 1 femoral vein. Bradycardia was consistently demonstrated by closing the fistulas. In some animals this bradycardia was abolished by carotid sinus denervation alone, the aortic arch receptors remaining intact; in others, bradycardia was abolished by aortic arch receptor denervation alone, the carotid sinus remaining intact. Furthermore, the "rebound effect" in arterial pressure and heart rate which follows quick closure of an arteriovenous fistula was abolished by combined denervation of the carotid sinus and aortic arch. This would seem to indicate that in any individual dog both pressoreceptors on the arterial side of the circulation (carotid sinus or aortic arch) may be receptive or either may be dominant.

KRAUSE

Montgomery, H.: Oxygen Tension of Peripheral Tissue. Am. J. Med. 23: 697 (Nov.), 1957.

The polarographic method was used to measure the rate of delivery of oxygen to an electrode in human skin or muscle. Such a method may indirectly give data on changes of blood flow, tissue metabolism, and arterial oxygen tension. Marked changes in skin oxygen tension are produced by even moderate reflex cutaneous dilatation or vasoconstriction. Direct heating and cooling of the skin also affect cutaneous oxygen tension and

bloo flow with maximum oxygen tension at 40 to 4 C. Passive dependent position of a limb inc sed blood flow and oxygen tension of skin and uscle. The effects of Buerger's exercises and oscillating bed were studied. Epinephrine and ntravenous priscoline and Ilidar increased skin low and oxygen tension. Increased environmel oxygen concentration and oxygen inhalatio have also been shown to affect the skin oxy n tension of healthy and diseased limbs.

KURLAND

Fu man, F. A., and Fuhrman, G. J.: The Treatnt of Experimental Frostbite by Rapid Tawing. A Review and New Experimental Ita. Medicine **36**: 465 (Dec.), 1957.

Cold injury may occur with or without the formaton of ice in the tissues. Trench foot and immersion foot are examples of such injury without the actual formation of ice in tissues. Frostbite denotes true freezing, with ice crystals forming in the tissues. Much of the earlier literature is ambiguous in differentiating these 2 forms of cold injury. The authors review the history of the treatment of cold injury and in particular attempt to trace the origins of the widespread belief that rapid thawing is dangerous and that application of snow or cold water is preferable. This belief has been deeply rooted in most parts of the world for may centuries though there are a few small areas where it has been traditional to avoid snow or ice and to use warmth. The first modern experiments comparing slow and rapid thawing were performed in 1937. Since then there have been many studies including the authors. These studies all indicated that rapid thawing is the method of choice in experimental frostbite. When frostbite occurs ice crystals form in the tissues, thereby removing pure water from solution and resulting in increased electrolyte concentration. Whether the ice crystals form within or outside the cell, water passes through the cell membranes because of the osmotic pressure differenc. Damage results from the action of concentrated electrolyte solutions on the cell membrane. Rapid thawing is beneficial not only by virtue of decreasing the duration of the frozen state, but also by decreasing the time during which damage to the cells can be done by the high electrolyte concentrations. The most effective method of rapid thawing is immersion of the frozen part in water at 2 ± 2 C. for a time sufficient to restore approximately normal deep tissue temperature. Prolonged warming is harmful. Rapid thawing is most effective after frostbite of brief duration.

ENSELBERG

Shanbrom, E., and Levy, L.: The Role of Systemic Blood Pressure in Cerebral Circulation in Carotid and Basilar Artery Thromboses. Clinical Observations and Therapeutic Implications of Vasopressor Agents. Am. J. Med. **23**: 197 (Aug.), 1957.

The relation of systemic blood pressure to brain circulation was studied in 2 patients in whom cerebral blood flow was impaired by obliterative disease of the carotid or basilar system. Although neither patient was known to have had hypertension, a decrease in blood pressure to normotensive levels resulted in the clinical picture of cerebral ischemia. By the use of vasopressor agents it was possible to maintain the minimal level of arterial pressure (160 and 140 mm. Hg systolic) necessary to overcome ischemia and reduce focal neurologic symptoms.

KURLAND

Corday, E., and Rothenberg, S. F.: The Clinical Aspects of Cerebral Vascular Insufficiency. Ann. Int. Med. **47**: 626 (Oct.), 1957.

Acute cerebral vascular insufficiency can be considered to be a definite physiologic disturbance resulting from a deficiency of blood through the cerebral arteries as a result of inadequate systemic blood pressure or to a decrease in cardiac output usually in the presence of cerebral arterial narrowing. Quite often, the condition is transitory and reversible; however, permanent cerebral damage can result if the disturbance is not properly corrected. A reduction of systemic arterial blood pressure is capable of causing focal or generalized cerebral ischemia by reducing the blood flow through narrowed cerebral arteries, especially if the reduction of systemic pressure is so pronounced that the collateral circulation cannot maintain adequate blood flow. Experiments in monkeys and observations in man have demonstrated clearly that the systemic blood pressure and the cardiac output must be maintained in patients with narrowed cerebral arteries in order to avert a serious cerebral insult. There is a discussion of 23 clinical conditions in which the phenomenon of cerebral vascular insufficiency has been observed: in states of shock, as a result of the excessive use of antihypertensive drugs, in postsympathectomy states, with hypersensitivity of the carotid sinus, postural hypotension, reflex hypotensive episodes, cardiac arrhythmias, surgical procedures, anesthesia, congestive heart failure, pulmonary hypertension, vasodilatation due to heat, valsalva maneuver, gravitational effects, angiography, hypothermia, sleep in the erect position, labyrinthitis, and pulmonary embolism. In

all of these conditions, systemic hypotension, reduction of cardiac output, or diversion of blood from the brain has occurred in the presence of cerebral vascular narrowing.

WENDKOS

Soloff, L. A., Zatuchni, J., Stauffer, H. M., and Tyson, R. R.: Venous Angiocardiographic Diagnosis of Acute Dissecting Hematoma of Aorta (Dissecting Aneurysm). Arch. Surg. **76:** 116 (Jan.), 1958.

Now that acute dissecting hematoma of the aorta is potentially curable by surgery there is a great need for a reliable and safe diagnostic procedure that can establish the diagnosis beyond question immediately after the onset of symptoms. The authors cite their experiences with venous angiocardiography in 3 patients with acute dissecting hematoma of the aorta and in a fourth patient with a combination of an aneurysm of the aorta and healed dissecting hematoma. One of the patients with acute dissecting hematoma had a successful surgical repair of the lesion following angiocardiographic confirmation of the diagnosis. Two others refused operation. In the fourth patient with the combination of aneurysm and healed dissecting hematoma, necropsy confirmed the angiocardiographic findings. In these 4 patients the authors encountered no untoward cardiac or aortic reaction and the studies were diagnostic. The diagnostic venous angiocardiographic pattern of acute dissecting hematoma and a variation of this pattern produced by an associated aneurysm are described. The authors recommend venous angiocardiography as a safe diagnostic procedure in the presence of acute dissecting hematoma of the aorta.

BROTHERS

Greisman, S. E.: Capillary Observations in Patients with Hemorrhagic Fever and Other Infectious Illnesses. J. Clin. Invest. **36:** 1688 (Dec.), 1957.

By direct microscopy, alterations in the nailfold capillary bed in patients acutely ill with hemorrhagic fever and with other infectious diseases were followed serially and correlated with the clinical course. Although single observations were of limited value because of individual variations, when considered collectively, the changes assumed certain patterns. During the febrile and hypotensive phases of illness, decreased vasomotor activity and refractoriness to l-norepinephrine, dilatation, and hemorrhagic diathesis were observed. These findings in hemorrhagic fever were significantly different when compared to patients with other infectious illnesses. These changes were not specific, however, and appear to represent a general response pattern to a number of infectious agents that act primarily upon the capillary vascular system. Capillary constriction at the nail fold and heightened vasomotor activity, as occur during the hypertensive phase of hemorrhagic fever, appear to be specific for this infectious disease.

WAI[illegible]

McDevitt, E., Carter, S. A., Gatje, B. W., Fr[illegible]ey, W. T., and Wright, I. S.: Use of Anticoagulants in Treatment of Cerebral Vascular Disease. J.A.M.A. **166:** 592 (Feb. 8), 1958.

Fifty-one patients with rheumatic heart disease, 28 with arteriosclerotic or hypertensive heart disease, and 11 with miscellaneous diagnoses were followed on and off anticoagulants for a total of 5,133 patient months or 428 patient years. During 2,842 patient months without anticoagulant therapy there were 229 thromboembolic episodes of which 67 were cerebral as compared with 20 thromboembolic episodes (5 being cerebral) that occurred during 2,291 patient months on anticoagulant therapy. With interrupted anticoagulant therapy it was found that 48 thromboembolic episodes occurred during 1,311 patient months as compared with 15 episodes during 957 patient months on continuous therapy. Hemorrhagic complications were infrequent and rarely serious. It is thought that continuous anticoagulant therapy can markedly reduce the incidence of thromboembolic episodes due to various primary conditions without unduly high risk of serious complications.

KITCHELL

Crane, C.: Embolism to the Bifurcation of the Aorta. New England J. Med. **258:** 359 (Feb. 20), 1958.

Fourteen cases of embolism to the bifurcation of the aorta in whom embolectomy was performed are reviewed. There were 4 deaths and 2 patients required low-thigh amputation. A total of 36 other arterial emboli before, during, or after aortic embolism in these patients thus emphasizing the frequency of lesser arterial embolism in these patients. In suitable cases prompt mitral valve surgery is indicated after a warning embolism. Certain technical considerations in the operative procedure designed to permit as thorough removal as possible of all thrombo[illegible] serious consideration of early embolectomy [illegible] material are described.

SAGALL

AMERICAN HEART ASSOCIATION, INC.

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ASSOCIATION AWARDS PRESENTED AT ANNUAL SCIENTIFIC SESSIONS

Among the honors conferred on physicians at the Scientific Sessions in San Francisco by the American Heart Association for outstanding service in advancing the Heart program and for achievement in cardiovascular research were the following:

GOLD HEART AWARDS

Recipients of the Gold Heart Awards, highest award of the Heart Association for outstanding contributions to cardiovascular medicine and the heart organization were E. Cowles Andrus, M.D., past-President of the American Heart Association, and William F. Hamilton, Ph.D., Professor of Physiology, Medical College of Georgia, Augusta.

Dr. Andrus, Associate Professor of Medicine, Johns Hopkins University Medical School, has been an outstanding leader in the activities of the American Heart Association since 1933. He has served several terms on the Association's Board and Executive Committee and has been chairman of the Executive Committee of the Scientific Council, of the Committee to Review Research Policy, and of the Budget Committee. Dr. Andrus presently serves on the Editorial Board of *Circulation*.

Dr. Hamilton was cited for his contributions to scientific knowledge of the circulation, including the development of a method for accurate measurement of blood volume, and for his pioneering efforts in the training of young investigators in cardiovascular research techniques. A former member of the Association's Board and Executive Committee Dr. Hamilton has served for many years on the various scientific councils and committees of the American and Georgia Associations.

LASKER AWARD

Irvine H. Page, M.D., Director of Research at the Cleveland Clinic, received the Albert Lasker Award of the American Heart Association for distinguished achievement in the field of cardiovascular research and especially for his many contributions to the knowledge of the basic mechanisms of hypertension. Tribute was paid to Dr. Page for his part in the discovery and synthesis of angiotensin, for his isolation of serotonin, and for "his gift of scientific leadership," which "has left its mark on many other areas of cardiovascular research."

Dr. Page, who is past-President of the American Heart Association, the Cleveland Area Heart Society, and the American Society for the Study of Arteriosclerosis, was a prime mover in the organization of the Heart Association's Council for High Blood Pressure Research. He served as the Council's first Medical Advisory Chairman and is presently a member of its Executive Committee. Also a member of the Board of Directors of the American Heart Association, Dr. Page is the author of many articles and books on hypertension and other aspects of cardiovascular disease. He has also contributed a chapter to "You and Your Heart," a popular volume on heart disease for the general public.

The Lasker Award, which is given annually by the Albert and Mary Lasker Foundation through the American Heart Association, consists of a statuette of the *Winged Victory of Samothrace* and an honorarium of $2,500.

AHA AFFILIATES AND CHAPTERS AID NATIONAL RESEARCH PROGRAM

Affiliates and chapters of the American Heart Association have provided nearly

$93,000 to help underwrite the record total of $3,062,204 awarded for the 1958-59 fiscal year under the Association's national research support program. The additional support, which helps to reduce a deficit in the national grants-in-aid budget, was in response to urgent requests sent to Heart Associations by Robert D. Wilkins, M.D., AHA President, and A. C. Corcoran, M.D., Chairman of the Association's Research Committee.

The new sums, all of which are applied to AHA-supported grants and fellowships, are in addition to funds affiliates and chapters regularly assigned to the national research program.

Recipients of AHA grants-in-aid which were supported in full or in part by local Heart Associations were listed in the September issue of *Circulation*. In addition, the following Associations have provided research funds:

Texas Heart Research Foundation, in full support of the grant-in-aid of Walter S. Henly, Established Investigator at Baylor University College of Medicine, Houston; Stamford-Darien, New Canaan (Conn.) Heart Association, partial support of the grants of Franklin H. Epstein and William L. Glenn at Yale University School of Medicine; Hartford (Conn.) Heart Association, partial support of the grant of Averill A. Liebow, also at Yale; Idaho Heart Association, partial support of the grant of John J. Osborn, Stanford University Hospital, San Francisco; and Delaware Heart Association, in full support of the grant to William S. Blakemore at the University of Pennsylvania School of Medicine.

Funds to be applied by the National Office on an unrestricted basis have also been made available by the Appalachian Area (Tenn.) Heart Committee; Boyd County (Ky.) Heart Association; Connecticut Heart Association; East Tennessee Heart Association; Memphis (Tenn.) Heart Association; Montana Heart Association; Tennessee Heart Association; and West Tennessee Heart Association.

RESEARCH CAREERS TV SERIES NOW BEING SHOWN ON FILM

Kinescopes selected from the educational television series "Decision for Research," presented by the American Heart Association and its affiliates and NBC-TV to stimulate the interest of young people in research careers, are now being shown to students and educators by Heart Associations throughout the country.

The filmed programs are designed to acquaint high school and junior college students with the nature of medical and biological research being undertaken by leading cardiovascular investigators who discuss and demonstrate investigations under way in their laboratories. The programs were originally televised as 13 weekly half-hour shows over stations of the Educational Television Network and many NBC-TV stations in cooperation with the Educational Television and Radio Center and the National Broadcasting Company. This series was made possible by a generous grant from E. R. Squibb and Sons, a division of Olin Mathieson Chemical Corporation.

FILMS OF LAY SERIES ON CARDIOVASCULAR SYSTEM AVAILABLE TO SPEAKERS

Two new films, "Varicose Veins" and "Circulation of the Blood," continuing a series on the cardiovascular system and its diseases which may be used as visual aids by physicians when addressing lay groups, are available from local Heart Associations or from the American Heart Association.

"Varicose Veins," seven minutes long, shows by means of animated diagrams the structure and function of the vein's valves and how their malfunction may cause varicosity. The script follows closely the text of the booklet *Varicose Veins* issued by the Association last year for distribution by physicians to their patients.

"Circulation of the Blood," eight and one half minutes long, consists of a series of diagrammatic drawings which trace the blood circulation and explain how expansion and

contraction of the arteries control its flow.

Both films, which may be used for television or direct audience viewing, were produced for the American Heart Association and its affiliates by Churchill-Wexler Film Production. Earlier films in the series include "High Blood Pressure," "Strokes" and "Coronary Heart Disease."

HIGH BLOOD PRESSURE RESEARCH COUNCIL MEETING IN CLEVELAND, NOVEMBER 21-22

The Association's Council for High Blood Pressure Research has scheduled its annual conference in Cleveland on Friday, November 21 and Saturday, November 22, 1958.

A tentative program includes discussion of "Chlorothiazide and Altered Vascular Responsiveness," and "Extra-Cellular Fluid and Plasma Volume Changes." Discussion at a business meeting on Friday afternoon will include "Labor Force of a Chicago Utilities Organization," and "The Framingham Project." The Council's Annual Dinner is scheduled for Friday evening.

MEETINGS CALENDAR

November 14-15: First Annual Symposium of Cinefluorography, Rochester, N.Y. George H. Ramsey, Department of Radiology, Strong Memorial Hospital, Rochester 20, N.Y.

November 21-22: American Heart Association's Council for High Blood Pressure Research, Cleveland. John Peters, American Heart Association, 44 East 23rd Street, New York 10, N.Y.

November 20-22: American College of Cardiology, Interim Meeting, New Orleans. Philip Reichert, Empire State Building, New York 1, N.Y.

December 12-13: American Federation for Clinical Research, Eastern Section, Boston. William B. Schwartz, New England Center Hospital, 171 Harrison Avenue, Boston 11, Mass.

January 22-24: American Federation for Clinical Research, Southern Section, New Orleans. Ellard M. Yow, Baylor University College of Medicine, Houston 25, Tex.

January 28-29: American Federation for Clinical Research, Western Section, Carmel, Calif. Richard J. Havel, University of California Medical Center, San Francisco 22, Calif.

March 17-19: National Health Council, Chicago. Philip E. Ryan, 1790 Broadway, New York 19, N.Y.

April 6-9: American Academy of General Practice, San Francisco. Mac F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.

April 15-17: American Surgical Association, San Francisco. W. A. Altemeier, Cincinnati General Hospital, Cincinnati 29, Ohio.

April 20-24: American College of Physicians, Chicago. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

ABROAD

November 30-December 3: Fourth Latin-American Congress of Angiology, Santiago, Chile. Juan Borzone Galvez, Cassila 10256, Santiago, Chile.

February 19-21: Central Surgical Association, Montreal Canada. A. D. McLachlin, Victoria Hospital, London, Ontario, Canada.

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why all the fuss over potassium?

Many physicians will recall when safe but potent organomercurials were first introduced. At the time there was considerable worry about possible potassium loss. Patients were instructed to take foods rich in this mineral, and not infrequently potassium supplements also were advised. After enough experience was gained, it became evident that only the exceptional case could lose enough potassium to be concerned about. And with oral organomercurial diuretics this was practically never a problem.

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